533 Rec'd PCT/PTO 07 AUG 2000 U 012894-7

09/601751

Practitioner's Docket No. U 012883-2

CHAPTER II

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US)

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/SE99/00511	MARCH 30, 1999	MARCH 31, 1998

TITLE OF INVENTION

AN APPARATUS FOR CONTROLLING THE GENERATION OF ELECTRIC FIELDS

APPLICANT(S)

1. BERTIL R.R. PERSSON
2. BERNT J. BÖHMER
3. BO H.G. THORVINGER

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231
ATTENTION: EO/US

NOTE: The completion of those filing requirements that can be made at a time later than 30 months from the priority date results from the Commissioner exercising his judgment under the authority granted under 35 USC 371(d). The filing receipt will show the actual date of receipt of the last item completing the entry into the national phase. See 37 C.F.R. §1.491 which states: "An international application enters the national state when the applicant has filed the documents and fees required by 35 USC 371(c) within the periods set forth in § 1.494 and § 1.495."

CERTIFICATION UNDER 37 C.F.R. 1.10*
*(Express Mail label number is **mandatory**.)*
(Express Mail certification is optional.)

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on this date August 7, 2000, in an envelope as "Express Mail Post Office to Addressee," Mailing Label Number EL386270495US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

CONNIE YANNOTTI
(type or print name of person mailing paper)

Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

****WARNING:*** *Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

EXPRESS MAIL LABEL NO.: EL386270495US

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. §1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing - See 37 C.F.R. §1.8.*

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 USC 371 otherwise the submission will be considered as being made under 35 USC 111. 37 C.F.R. § 1.494(f).

1. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. 371:

   a. [X] This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).

   b. [X] The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2.Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
[ ]*	TOTAL CLAIMS	18 - 20 =	0	x $ 18.00 =	$ 0
	INDEPENDENT CLAIMS	1 - 3 =	0	x $ 78.00 =	0
	MULTIPLE DEPENDENT CLAIM(S) (if applicable) + $260.00				
BASIC FEE**	[ ] U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: [ ] and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(2) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 CFR 1.492(a)(4)) ..... $96.00 [ ] and the above requirements are not met (37 CFR 1.492(a)(1)) ..... $670.00 [X] U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: [ ] has been paid (37 CFR 1.492(a)(2)) ..... $690.00 [X] has not been paid (37 CFR 1.492(a)(3)) ..... $970.00 [ ] where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 CFR 1.492(a)(5)) $840.00				
	Total of above Calculations				970
SMALL ENTITY	Reduction by ½ for filing by small entity, if applicable. Affidavit must be filed. (note 37 CFR 1.9, 1.27, 1.28)				-485.00
	Subtotal				485.00
	Total National Fee				$485.00
	Fee for recording the enclosed assignment document $40.00 (37 CFR 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				
TOTAL	Total Fees enclosed				$485.00

*See attached Preliminary Amendment Reducing the Number of Claims.

i. [X] A check in the amount of $485.00 to cover the above fees is enclosed.
ii. [ ] Please charge Account No. _____ in the amount of $ _____.
A duplicate copy of this sheet is enclosed.

**WARNING: *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. [X] A copy of the International application as filed (35 U.S.C. 371(c)(2)):

NOTE: *Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.*

a. [ ] is transmitted herewith.
b. [ ] is not required, as the application was filed with the United States Receiving Office.
c. [X] has been transmitted
i. [X] by the International Bureau.
Date of mailing of the application (from form PCT/IB/308): OCT. 21, 1999
ii. [ ] by applicant on _____ (Date).

4. [X] A translation of the International application into the English language (35 U.S.C. 371(c)(2)):
a. [X] is transmitted herewith.
b. [ ] is not required as the application was filed in English.
c. [ ] was previously transmitted by applicant on _____ (Date).
d. [ ] will follow.

5. [X] Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. 371(c)(3)):

NOTE: The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.

a. [ ] are transmitted herewith.
b. [ ] have been transmitted
   i. [ ] by the International Bureau.
   Date of mailing of the amendment (from form PCT/IB/308): _____.
   ii. [ ] by applicant on _____.
   Date
c. [X] have not been transmitted as
   i. [X] applicant chose not to make amendments under PCT Article 19.
   Date of mailing of Search Report (from form PCT/ISA/210): Jan 12, 1999.
   ii. [ ] the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. [X] A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. 371(c)(3)):
   a. [ ] is transmitted herewith.
   b. [ ] is not required as the amendments were made in the English language.
   c. [X] has not been transmitted for reasons indicated at point 5(c) above.

7. [X] A copy of the international examination report (PCT/IPEA/409)
   [X] is transmitted herewith.
   [ ] is not required as the application was filed with the United States Receiving Office.

8. [X] Annex(es) to the international preliminary examination report
   a. [X] is/are transmitted herewith.
   b. [ ] is/are not required as the application was filed with the United States Receiving Office.

9. [X] A translation of the annexes to the international preliminary examination report
   a. [X] is transmitted herewith.
   b. [ ] is not required as the annexes are in the English language.

10. [X] An oath or declaration of the inventor (35 U.S.C. 371(c)(4)) complying with 35 U.S.C. 115
    a. [ ] was previously submitted by applicant on _____. Date
    b. [X] is submitted herewith, and such oath or declaration
        i. [ ] is attached to the application.
        ii. [X] identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. 1.70.
    c. [ ] will follow.

Other document(s) or information included:

11. [X] An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):
    a. [X] is transmitted herewith.
    b. [ ] has been transmitted by the International Bureau.
    Date of mailing (from form PCT/IB/308): _____.
    c. [ ] is not required, as the application was searched by the United States International Searching Authority.
    d. [ ] will be transmitted promptly upon request.
    e. [ ] has been submitted by applicant on _____. Date

12. [X] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98:
    a. [ ] is transmitted herewith.
    Also transmitted herewith is/are:
    [ ] Form PTO-1449 (PTO/SB/08A and 08B).
    [ ] Copies of citations listed.
    b. [X] will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).
    c. [ ] was previously submitted by applicant on _____. Date

13. [X] An assignment document is transmitted herewith for recording.

A separate [X]"COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or [ ] FORM PTO 1595 is also attached.

_____
_____
_____

14. [X] Additional documents:
    a. [X] Copy of request (PCT/RO/101)
    b. [X] International Publication No. WO 99/52589
        i. [X] Specification, claims and drawing
        ii. [ ] Front page only
    c. [X] Preliminary amendment (37 C.F.R. § 1.121)
    d. [X] Other

    FORM PCT/IB/308
    SIXTEEN SHEETS OF DRAWINGS (FORMAL)

15. [X] The above checked items are being transmitted
    a. [X] before 30 months from any claimed priority date.
    b. [ ] after 30 months.

16. [ ] Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____, namely:

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).

[X] The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 12-0425 .

[X] 37 C.F.R. 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

[ ] 37 C.F.R. 1.492(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must

only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.

[X] 37 C.F.R. 1.17 (application processing fees)
[X] 37 C.F.R. 1.17(a)(1)-(5)(extension fees pursuant to § 1.136(a).
[X] 37 C.F.R. 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. 1.311(b))

NOTE: *Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).*

NOTE: *37 C.F.R. 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.*

[ ] 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

J H Cohen
Reg. No. 20,302

SIGNATURE OF PRACTITIONER

Reg. No.: 20302

JULIAN H. COHEN
(type or print name of practitioner)

Tel. No.: (212)

LADAS & PARRY
P.O. Address

Customer No.:

26 WEST 61ST STREET
NEW YORK, NEW YORK 10023

Practitioner's Docket No. U 012894-7 ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

[X] In re application of: PERSSON, Bertil; BÖHMER, Bernt and THORVINGER, Bo
Application No.: Group No.:
Filed: Examiner:
For: An Apparatus for Controlling the Generation of Electric Fields

[ ] *Patent No.: Issue Date:

**NOTE: Insert name(s) of inventor(s) and title also for patent Where statement is with respect to a maintenance fee payment, also insert application number and filing date, and add Box M. Fee to address.*

STATEMENT CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(c-f) and 1.27(b-d))

With respect to the invention described in
[ ] the specification filed herewith.
[ ] application no. _____, filed _____.
[ ] patent no. _____ issued _____.

I. IDENTIFICATION AND RIGHTS AS A SMALL ENTITY

I hereby state that I am

(complete either (a), (b), (c) or (d) below)

(a) Independent Inventor
[ ] a below named independent inventor, and that I qualify as an independent inventor, as defined in 37 CFR 1.9(c), for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark Office.

(b) Noninventor Supporting a Claim by Another
[ ] making this statement to support a claim by

_____
for a small entity status for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code. I hereby state that I would qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code, if I had made the above identified invention.

(c) Small Business Concern
[X] the owner of the small business concern identified below:
[ ] an official of the small business concern empowered to act on behalf of the concern identified below:

Name of Concern ADITUS MEDICAL AB

EXPRESS MAIL LABEL NO.: EL386270475US

Address of Concern Bålabäcksvägen 1
SE-240 36 STEHAG and

that the above identified small business concern qualifies as a small business concern, as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

(d) Non-Profit Organization

[ ] an official empowered to act on behalf of the nonprofit organization identified below:

Name of Organization _____
Address of Organization _____
_____

TYPE OF ORGANIZATION

[ ] University or Other Institution of Higher Education

[ ] Tax Exempt Under Internal Revenue Service Code (26 USC 501(a) and 501(c) (3))

[ ] Nonprofit Scientific or Educational Under Statute of State of the United States of America
(Name of State _____)
(Citation of Statute _____)

[ ] Would Qualify as Tax Exempt Under Internal Revenue Service Code (26 USC 501(a) and 501(c) (3)), if Located in the United States of America

[ ] Would Qualify as Nonprofit Scientific or Educational Under Statute of State of the United States of America, if Located in the United States of America
(Name of State _____)
(Citation of Statute _____)

and that the nonprofit organization identified above qualifies as a nonprofit organization, as defined in 37 CFR 1.9(e), for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code.

II. OWNERSHIP OF INVENTION BY DECLARANT

I hereby state that rights under contract or law remain with and/or have been conveyed to the above identified

[ ] person	[X] concern	[ ] organization
(item (a) or (b) above)	(item (c) above)	(item (d) above)

EXCEPT, that if the rights held are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held (1) by any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, (2) any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or (3) a nonprofit organization under 37 CFR 1.9(e).

[X] no such person, concern, or organization
[ ] person, concerns or organizations listed below*

**NOTE: Separate statements are required from each named person, concern or organization having rights to the invention as to their status as small entities. (37 CFR 1.27)*

Full Name _____
Address _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

Full Name _____
Address _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

III. ACKNOWLEDGEMENT OF DUTY TO NOTIFY PTO OF STATUS CHANGE

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

IV. DECLARATION

(check the following item, if desired)

NOTE: The following verification statement need not be made in accordance with the rules published on October 10, 1997, 62 Fed. Reg. 52131, effective December 1, 1997.

NOTE: "The presentation to the Office (whether by signing, filing, submitting, or later advocating) of any paper by a party, whether a practitioner or non-practitioner, constitutes a certification under § 10.18(b) of this chapter. Violations of § 10.18(b)(2) of this chapter by a party, whether a practitioner or non-practitioner, may result in the imposition of sanctions under § 10.18(c) of this chapter. Any practitioner violating § 10.18(b) may also be subject to disciplinary action. See §§ 10.18(d) and 10.23(c)(15)." 37 CFR 1.4(d)(2).

[ ] I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

V. SIGNATURES

(complete only (e) or (f) below)

(e)
NOTE: All inventors must sign the statement.

_____ Date:_____
Name of Inventor

_____
Signature of Inventor

_____ Date:_____
Name of Inventor

_____
Signature of Inventor

_____ Date:_____
Name of Inventor

_____
Signature of Inventor

(add lines for any additional inventors who must sign)

or

(f)
NOTE: The title of the person signing on behalf of a concern or nonprofit organization should be specified.

Name of Person Signing 1) BO THORVINGER, 2) BERTIL PERSSON, 3) Bernt Behncr

Title of Person Member of the board Member of the board Member of the board
(if signing on behalf of a concern or non-profit organization)

Address of Person Signing See below

SIGNATURE See below DATE July 17, 2000

1)
Humlebäcksgatan 43
SE-216 20 Malmö
Sweden

2)
Angantyrsgränd 19
SE-224 75 Lund
Sweden

3)
Bålabäcksvägen 1
SE-240 36 Stehag
Sweden

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application: BERTIL R.R. **PERSSON**, et al

For: AN APPARATUS FOR CONTROLLING THE GENERATION OF ELECTRIC FIELDS

Attorney Docket No.: U 012883-2

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Please amend the above application as follows:

IN THE CLAIMS

Claim 3, line 1, delete "or 2"

Claim 4, line 1, delete "any of the preceding Claims" and replace therefor

-- claim 1--

CERTIFICATE UNDER 37 1.10

I hereby certify that this paper is being deposited with the United States Postal Service on this date AUGUST 7, 2000 in an envelope as "EXPRESS MAIL POST OFFICE TO ADDRESSEE" Mailing Label Number EL386270495US addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231

CONNIE YANNOTTI
(Type or print name of person mailing paper)

Connie Yannotti
(Signature of person mailing paper)

NOTE: Each paper or fee referred to as enclosed herein has the number of the "EXPRESS MAIL" mailing label place thereon prior to mailing 37 CFR 1.16(b).

Claim 5, line 1, delete "any of the preceding Claims" and replace therefor -- claim 1--

Claim 6, line 1, delete "any of the preceding Claims" and replace therefor -- claim 1--

Claim 7, line 1, delete "any of the preceding Claims" and replace therefor -- claim 1--

Claim 8, line 1, delete "any of the preceding Claims" and replace therefor -- claim 1--

Claim 9, line 1, delete "any of the preceding Claims" and replace therefor -- claim 1--

Claim 10, line 1, delete "any of the preceding Claims" and replace therefor -- claim 1--

Claim 11, line 1, delete "any of the preceding Claims" and replace therefor -- claim 1--

~~Claim 12, line 1, delete "any of the preceding Claims" and replace therefor -- claim 1--~~

Claim 16, line 1, delete "any of Claims 1-10" and replace therefor

-- claim 1--

Claim 17, line 1, delete "any of the preceding Claims" and replace therefor

-- claim 1--

Claim 18,line 1, delete "any of the preceding Claims" and replace therefor

-- claim 1--

Respectfully submitted,

JH Cohen
Reg No. 25,858

JULIAN H. COHEN
LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG.NO.25858(212)708-1930

16/PRTS

AN APPARATUS FOR CONTROLLING THE GENERATION OF ELECTRIC FIELDS

The present invention relates to an apparatus for generating pulses of electric fields in a restricted area of a human or an animal according to the preamble to the appended independent Claim.

The therapy forms which are routinely employed in modern medical care for tumor therapy are examples of treatment types where the outcome of such treatment is unsatisfactory. For example, in tumor therapy unsuccessful attempts are often made to achieve local tumor control, which is the cause of mortality of approximately 30% of cancer patients. It is, therefore, important to develop a new and improved technique for local and regional tumor treatment.

In today's medical care, surgery, chemotherapy and radiation therapy, also known as radiation treatment, or combinations hereof are the most commonly employed methods for treating malignant tumors. Approximately every second patient suffering from infiltrating cancer is treated with radiation therapy, but only roughly half of the patients are cured. This failure is, on the one hand, the cause of the presence of widespread disease (distal metastasis) or relapses (the return of tumors in the treated area), and on the other hand because certain types of tumor are resistant to radiation treatment or chemotherapy.

With varying success, attempts have been made to reinforce and improve the efficiency of radiation therapy in sterilizing tumors. For example, use has been made of more sophisticated radiation therapy techniques, such as stereotactic treatment, "conformal radiotherapy", of altered fractioning or added pharmaceuticals to increase the radiation sensitivity of the tumors.

Use is also made of heat as an adjuvant ionizing radiation, which, for certain tumor forms, may increase the number of complete remissions by up to a factor of two.

Also in certain purely medically treated diseases in local organs, the outcome of treatment is occasionally insufficient. It is obvious that, in addition to the wishes which exist regarding improved techniques for treating, for example, tumors, there are not only wishes but also needs for a more efficient technique for treating certain other diseases. In, for example, the local treatment of local organs or tumors, it is a major advantage if, on each treatment occasion, it is possible to adapt the intensity of the treatment to suit the status of the tissue in the local region or in the organ being treated.

According to the present invention, use is made of a series of brief high voltage pulses for generating electric fields in the local region or in the organ which is to be treated. In the continuation of this description, use will also be made of the expression High Voltage Impulse Therapy, occasionally abbreviated to HVIT.

The treatment with electric fields realizes a perforation of the cell membranes which thereby allow the passage of substances (e.g. cytostatic or genetic material) added to the body. The treatment involves increased inflow of therapeutic substances, whereby the effects of chemotherapy are amplified. The outflow of specific substances out of, for example, tumor cells moreover often realizes a stimulation of the immune system. In total dielectric collapse, the result is often achieved that the cells are sterilized directly by the electric fields formed by the high voltage pulses. In clinical experiments, the method has proved to be effective in combination with cytostatics (Bleomycin) for, for example, treating melanoma and tumors in the neck, head, liver, pancreas and lungs.

In HVIT, the treatment result is determined by the number and duration of the high voltage pulses to which the tissue is subjected and how high electric field forces the impressed pulses create in the tissue, as well as the form or frequency the pulses possess. In order to achieve an effective and dependable treatment, it must be possible to control all of these physical parameters. Biological properties which affect the treatment result are, among other things, the electric conductive capacity of the tissue, its dielectric properties, the cell

sizes and the structures of the cell membranes. All of these properties vary between different tissues. In order to achieve optimum treatment effect, it is therefore necessary to measure how the electric properties of the tissue change between each high voltage pulse or between the series of pulses, i.e. to establish when the cells are sufficiently perforated.

In previously employed HVIT, it was not possible to monitor when the tissue was sufficiently perforated, i.e. when the treatment was completed, which entailed that the tissue was occasionally undertreated and occasionally overtreated. This involved a degree of uncertainty in the treatment result. A typical HVIT treatment according to prior art techniques entails that an applicator was placed over the tissue which was intended for treatment. The high voltage generator was, for example, set such that the outgoing voltage corresponded to a field force in the target volume of approx. 1300 V/cm. The treatment was completed with a fixed number of pulses which it was known normally gave the desired result. The weaknesses in this procedure were, on the one hand, that the size of the electric field which the generator in reality generated in the tissue of the target volume was unknown, and, on the other hand, that it was not possible to assess when the treatment was sufficient.

The present invention relates to an apparatus which includes mechanical devices for subjecting a tissue within a restricted region or an organ in a person or an animal for one or more pulses of an electric field at a field strength, configuration, duration and frequency adjustable for the relevant treatment occasion. The expression "duration" relates to both the length of the pulses and the number of pulses, the expression "frequency" relates to both how often the pulses are repeated and the frequency with which the field alternates during an ongoing pulse.

The characterizing clause of the appended independent Claim discloses a technique which entails a substantial improvement to the efficiency of surgery, chemotherapy and radiation therapy. The technique is also applicable within modern molecular medicine where substances and

genetic DNA sequences which are to be introduced into tissue cells are customized.

Further expedient embodiments of the present invention are disclosed in the appended subclaims.

The present invention will now be described in greater detail hereinbelow, with reference to a number of Figures, in which:

Fig. 1 is a block diagram of a fundamental apparatus for applying electric fields in a restricted region of a person or an animal;

Fig. 2 is a block diagram of a fundamental apparatus for applying electric fields and/or ionizing radiation in a restricted region of a human or an animal;

Fig. 3 is a block diagram of one embodiment of a combination of devices for forming electric fields in a restricted region of a human or an animal;

Figs. 4a-d are embodiments of electrode applicators for external treatment of tissue;

Fig. 5 shows one embodiment of an electrode applicator for intraoperative treatment of, for example, tumors and superficial tumor nodules;

Figs. 6a-d show embodiments of electrodes and electrode applicators designed for interstitial treatment of tissue;

Figs. 7a-c show embodiments of electrodes and electrode applicators designed for the treatment of, for example, tumors in bodily cavities and in organs accessible via large vessels;

Fig. 8 shows embodiments of electrodes in which these are disposed for combination treatment with antitumoral pharmaceutics;

Figs. 9a-e show examples of configurations of voltage pulses applied to the electrodes;

Fig. 10 is a simplified block diagram of one embodiment of the apparatus;

Fig. 11a shows a model of the principle structure of living tissue;

Fig. 11b is an electric skeleton diagram of the electric structure of living tissue; and

Fig. 12 is an electric model of a pulse generator connected to living tissue.

Fig. 1 shows, in block diagram, the basic design of a high voltage generator 1, electrodes 6,15,16,24 and a registration and conversion device 10, for example a computer or a microprocessor 10, these devices all being included in the apparatus according to the present invention. Hereafter, the word computer will also be employed without any restrictive intent for the registration and conversion device. Between the high voltage generator 1 and the electrodes 6,15,16,24, there are disposed one or more signal connections 32 and electric conductors 33. Between the computer 10 and the high voltage generator 1, and between the computer and the electrodes 6,15,16,24, there is provided one or more signal connections 32. While the signal connections 32 in the Figure are shown as directly connecting the computer and the electrodes, it will be obvious that the apparatus as such also includes devices described in the continued description of this application, such as switches 3, distributor 4, electrode applicator 5, etc. for controlling the voltage impressment of the electrodes, etc.

Fig. 2 shows one embodiment of the present invention in which a radiation transmitter 34 is connected via signal connections 32 to the

computer. In certain embodiments, the radiation transmitter is mechanically interconnected to the high voltage generator, while in other embodiments it only has signal connection with the combination of devices illustrated in Fig. 1.

Fig. 3 schematically shows one embodiment of a combination of devices for generating electric fields according to the present invention. The Figure shows blocks for a high voltage generator 1, a capacitor battery 2, a switch 3, a distributor 4 for distributing the high voltage pulses which are generated on discharge of the capacitor battery 2 through the switch 3 to an electrode applicator 5 and electrodes 6 intended to be placed in or adjacent the tissue region 7 or organ 7 of a patient undergoing treatment. The high voltage generator 1, the capacitor battery 2, the switch 3 and the distributor 4 are connected in series with one another by means of electric conductors 33. Between the distributor 4 and the electrode applicator 5, there is provided at least one electric conductor 33 and at least one signal connection 32. Via the signal connections 32, the distributor 4 controls the voltage impression of the electrodes of the electrode applicator, via which the electric conductors 33 are interconnected to the distributor 4 and via the electric conductor 33 to the switch 3. In one alternative embodiment, each electrode 6 is electrically connected to the switch 3 by means of an electric conductor 33.

As a rule, the distributor 4 or an electrode applicator impresses voltage simultaneously on only two electrodes 6, while the other electrodes are permitted to assume that potential which is determined by the placing of the electrode in the treatment region. The term voltage impression also includes in this context the fact that one or more electrodes are earthed (have zero potential). The switch 4 and/or the electrode applicator 5 are disposed to permit, if so wished, the voltage impression pairwise of all electrodes which are placed in the treatment region. It will be obvious to a person skilled in the art, that, in certain embodiments, the devices are provided in order, on voltage impression, to allocate to several electrodes a substantially corresponding (the same) potential.

All units are, via signal connections 32 which, in certain embodiments, are wholly or partly wireless, connected to a registration and conversion device 10 with a screen 10a. Hereafter, the designations control and conversion unit 10 or computer 10 will be employed for the registration and conversion device. The computer 10 constitutes a control and monitoring device for the function of the apparatus.

The expression electrode applicator 5 relates to a retainer member for the electrodes 6, where the retainer member is designed to facilitate the correct application of the electrodes at or in the treatment region.

The computer is set as a rule for the high voltage pulses to contain the following data:

repetition frequency	approx. 0.1-10000 per second
amplitude	approx. 50-6000V
pulse length	approx. 0.1-200 ms
number of pulses	1-2000 per treatment.

The pulses are applied before, during or immediately after the radiation treatment. Examples of pulse configuration employed are square pulse with a pulse length of 0.1-2 ms or exponentially fading pulse with a time constant RC approximately equal to 0.1-2 ms. In large amplitudes of the voltage, shorter pulse lengths are generally selected, and vice versa.

The high voltage generator 1 is, as a rule, disposed to emit modulated a.c. voltage of a frequency within a range of 40 Hz-2 MHz and as a rule within the range of 40 Hz-100 kHz. In those embodiments where the high voltage generator is disposed to emit a.c. voltage of high frequency, a modulator is employed instead of a capacitor battery and switch for generating short modulated high frequency pulses with a pulse length within the range of approx. 0.1-200 ms.

As will be apparent from the embodiment illustrated in Fig. 3, the apparatus generally also includes sensors 8 intended to be applied to

the patient in the treatment region. The sensors are connected via a detector interface 9 to the registration and conversion device 10. On application of the treatment pulse, a signal is generated in the sensors 8 which, via the interface 9, is transferred to and registered in the computer 10. From the measured signals, the computer calculates the electric field force induced by the pulse and the electromotive force in different parts of the treatment region 7. These signals entail that the computer 10 emits signals to the high voltage generator/capacitor battery (feedback) to adjust the amplitude of the generated pulses so that the predetermined field force is achieved in the treatment region. This monitoring and adjustment take place continuously during the application of the pulses.

Figs. 4a-d show embodiments of electrode applicators 5 for external treatment of a patient with the electrodes 6 applied in a restricted region on the patient and in different configurations around the tissue region 7, for example a tumor 7, which is to be treated. Figs. 4a and 4b show how by crosswise application of the electric high voltage pulses to different combinations of two electrodes 6, the result will be achieved, as marked in the Figure by the electric field force lines, that the electric field passes through all parts of the tissue region 7.

Figs. 4c-d show how electrodes are designed with abutment surfaces of different sizes in order for the field lines to be focused to the desired treatment region. At the beginning of the treatment, the electric high voltage pulses have, for example, a voltage which is adjusted in accordance with the distance between the electrodes. The voltage is then adjusted in accordance with the relationship:

Voltage = (constant) x (the distance between the pairwise electrodes). The value of the constant is varied in response to the type of tissue and is, as a rule, selected at values between approx. 500-3000 V/cm.

Once the treatment has commenced, the control unit and impedance measurement unit described below regulate the output voltage of the

pulse regulator to values which entail that the sought-for electric field force passes through the tissue.

Fig. 5 shows one embodiment of an electrode applicator 5 for intra-operative treatment, and treatment of, for example, superficial tumor nodules 7. The electrode applicator has a scissors-like design and comprises two shanks 12 of electrically insulating material (e.g. teflon) which are movably interconnected to one another in a journal 11. The shanks are provided with a gripping lock 13. At one end of each shank 12, the shanks are provided with finger grips and at the other ends with electrodes 6 which grasp about the tumor nodules 7. The grip locks 13 fix the shanks 12 in the set position. The voltage of the electric high voltage pulses is adjusted in response to the size of the tumor 7 with the aid of a distance sensor 14 built into the electrode applicator and connected to the computer 10. The voltage is set at the beginning of the treatment, for example according to the relationship:

Voltage = (constant) x (the distance between the pairwise electrodes). The value of the constant is adapted to the type of tumor and is, as a rule, selected within the range of approx. 500-3000 V/cm.

Once the treatment has commenced, the control unit and the impedance measurement unit described below regulate the output voltage of the pulse generator to values which entail that the sought-for electric field force passes through the tissue.

Figs. 6a-d show embodiments of electrodes 15,16 and a fixture 18 for the electrodes, where the electrodes and the fixture are suitable for use for interstitial treatment of both superficial and profound tissue. Fig. 6a shows the electrodes 15,16 in two different embodiments, namely in one embodiment in which the electrodes 15 are needle-shaped and in one embodiment in which the electrodes 16 are stiletto-shaped. Each one of the electrodes 15,16 is, in a portion 31 most proximal their one end, provided with an electric conductor 33 for connection to the high voltage generator 1. The above-mentioned portion is provided with an electrically insulating layer 17 or an electrically insulating sleeve 17 in which the electrode is inserted.

The electrodes are applied in different configurations in and about the tissue 7 or the organ 7 which is to be treated, either direct by free hand or with the aid of an electrode applicator (fixture) 18 provided with a hole. The electrode applicator is, as a rule, designed so as to be removed from the electrodes 15,16 once these have been applied on the patient. It will thereby be possible to allow the electrodes to remain in position in the patient to be used on several subsequent treatment occasions. Alternatively, the electrode applicator is removed together with the electrodes 15,16 after each treatment. Also in interstitial treatment, there are electrodes with surfaces of different sizes for controlling the extent of the electric fields.

Those parts of the electrodes 15,16 which are intended to be inserted into the patient to cover the extent of the tissue 7 which is to be treated are, for example, manufactured of stainless steel of a quality which agrees with or corresponds to that employed for injection syringes or are manufactured or coated with another tissue-friendly metal such as a noble metal, for example gold or platinum. The remaining portion of the electrodes forms an insulated portion 17 with input conductors 33 for the high voltage pulses. On the employment of flexible input conductors, the electrode is placed in a large cannula 19 which, after application of the electrode in the patient, is withdrawn, the electrodes remaining in position in the tissue.

In certain embodiments, the electrodes consist of radioactive metal (e.g. iridium-192, cobalt-60) or are surface coated with radioactive substances (e.g. iodine-125). In other embodiments, they are designed as tubes 20 of inert metal which are charged with radioactive material (e.g. ^{192}Ir, ^{137}Cs, ^{226}Ra) which advantageously takes place by the employment of a so-called after loading device 22. The pulses have a voltage which, at the start of the treatment, for example are determined by the distance between the electrodes. The voltage is then set according to the relationship:

Voltage = (constant) x (the distance between pairwise electrodes).

The value of the constant is selected in response to the type of

tumor and, as a rule, selected within the range of approx. 500-3000 V/cm.

Once the treatment has commenced, the control unit and the impedance measurement unit described below regulate the output voltage of the pulse generator to values which entail that the sought-for electric field force passes through the tissue.

In those applications where treatment with electric fields is combined with radiation treatment from a radiation source which is located outside the treatment region, the electrodes in the treatment region are supplied with electric voltage pulses before, during or immediately after the radiation treatment.

Figs. 7a-c show electrodes 24 for treating tissue accessible via, for example, major vessels, or via bodily cavities, for example respiratory tracts, urinary tracts and stomach-intestinal trait. The electrodes are disposed on the surface of a cylinder-like electrode applicator 23 of insulating material 17. In certain embodiments, the electrodes are designed such that they are introduced into the tissue through channels 25 in the applicator 23 operated by a remote control. As will be apparent from Fig. 7c, the channels 25 (according to the embodiment described in the preceding sentence) discharge in the circumferential surface of the electrode applicator, whereby the electrodes 24 are, on their displacement, guided into tissue surrounding the electrode applicator. In certain embodiments, the applicator is disposed to be supplied with radioactive preparations, whereby the applicator also forms a radiation device. The applicator is disposed to be supplied with the radioactive preparations manually or by means of an after loading device 22. The voltage of the electric high voltage pulses is adjusted during the treatment.

The field lines in Fig. 7a indicate the extent of the electric field lines in the tissue.

For intracavity treatment of tissue in different, irregularly shaped bodily cavities (e.g. oral cavity, respiratory tracts, oesophagus, stomach, uterus, bladder, ureter, rectum) electrode applicators 23 are

applied as is apparent from Figs. 7a-c, particularly designed in response to the configuration of the cavity, with electrodes applied on the surface 24 or alternatively designed as needles which, through channels 25, are passed into the tissue by remote control. These applicators are suitable for use when treating, for example, lung cancer, liver tumors, renal tumors and tumors in the stomach-intestines with reduced absorbed dose for reducing side effects of the radiation treatment in normal tissue. Prostate cancer is treated with applicators applied via the rectum and the ureter. These applicators are, in certain embodiments, designed to be charged with radioactive sources or radioactive material 21, either manually or using an after loading device 22.

Fig. 8 shows an apparatus for combined treatment with antitumoral pharmaceutics where the electrode 6 is coated with a layer 28 of porous metal, glass, ceramics, inert plastic or other polymer which contains antitumoral pharmaceuticals 29 (e.g. bleomycin, platinol, taxol, monoclonal antibodies), genetic material (chromosomes, DNA) or radioactive substances (e.g. iodine 125, Auger-electron emitters) 29. This type of electrode is well suited for use in radiation therapy, since the high electric field force increases the permeability of the tumor cell for the above mentioned substances and thereby increases the antitumoral effect.

Figs. 9a-e show examples of pulse forms in the voltage pulses which are pairwise applied to the electrodes 6,15,16,24. In the Figures the height of the pulse represents the voltage between two electrodes. The width of the pulse represents the length of the pulse. The Figures 9a and 9c show examples of square pulses, Figs. 9b and 9d examples of pulses whose voltage fades with time, and Fig. 9e pulses of alternating voltage. Figs. 9c and 9d show voltage pulses where, analogous to that which applies in alternating voltage, the electrodes alternatingly have the highest voltage, whereby a corresponding change takes place of the electric field between the electrodes.

The above described electrodes 6,15,16,24, the voltage generator 1, the control and converter device 10, also previously designated the

computer and an impedance measurement unit 50 are included in the block diagram shown in Fig. 10. The voltage generator, the computer, the electrodes and the impedance measurement unit are interconnected with one another by electric conductors for impressing voltage on the electrodes and for transferring signals. It will be obvious to a person skilled in the art that, in certain embodiments, at least a part of the signal connections are designed as wireless connections.

Fig. 11a shows the basic structure of living tissue, while Figure 11b shows an electric outline diagram for the electric structure of the tissue. The correspondences between the resistances and the capacitance in the electric diagram and in the tissue are apparent from the designations of the components and the continued description.

Fig. 12 shows the basic electric structure of a pulse generator 1, previously also designated high voltage generator. The Figure shows how the impedance of the tissue Z_{tissue} via the electrodes 6,15,16,24 is connected in series to the inner impedance of the pulse generator $Z_{generator}$. Reference letter U relates to electromotive force (EMF) of the pulse generator.

It will be obvious to a person skilled in the art that the above described mechanical units, in certain embodiments of the present invention, form mutually separate mechanical units which are interconnected with each other by means of electric conductors and signal connections, while, in other embodiments, some or all of these units, with the exception of the electrode applicator and the electrodes, form a mechanical unit which is co-ordinated with the voltage generator, the impedance measurement unit or the computer.

As will have been apparent from the foregoing description, the present invention relates to an apparatus for high voltage impulse therapy (HVIT) with detection of the treatment effect. The apparatus includes an impedance measurement unit which, on treatment of tissue or organs, is employed for measuring the electrical impedance of the tissue. The impedance measurement unit is, as a rule, disposed to measure the impedance of the tissue at, at least, one frequency. Normally, the

impedance measurement unit is disposed to measure the impedance of the tissue within a frequency range, e.g. within the range of 10 Hz to 10 Mhz. With the aid of a mathematical algorithm, a test magnitude is calculated whose value is a measurement of the treatment effect.

The voltage across the tissue will be in accordance with that shown in Fig. 12:

$$U_{tissue} = U_{generator} * Z_{tissue} / (Z_{tissue} + Z_{generator})$$

The impedance of the tissue varies extremely, depending upon the cell structure and build up of the tissue, the nature of the surrounding tissue and the quantity of bodily liquids which are found in and around the treated region. Since the output impedance of the generator is not slight in relation to the impedance of the tissue, the output voltage will vary greatly depending upon where and how the applicator is placed. It has proved, in practical experiments, that even if an applicator is placed at the same point, marked with a colour on the body, the impedance will vary greatly from time to time, depending upon minor differences in placing and contact impedance, as well as differences in fluid quantity and the nature of the tissue.

In order to be able to predict the actual pulse voltage from the pulse generator, the impedance of the tissue must be known at any time. Only if the output voltage from the generator is adjusted on the basis of the generator's output impedance and the impedance of the relevant tissue will it be possible to achieve a predictable and constant effect. According to the present invention, the apparatus includes means for measuring the impedance of the treated tissue and means for employing this information for controlling the output voltage of the pulse generator such that the desired field force is always achieved in the tissue.

Fig. 10 illustrates such a system. A control unit is included in the apparatus and measures, with the aid of the impedance measurement unit, the impedance of the tissue. The control unit adjusts the output voltage from the generator so that the desired field force is achieved.

In the control unit, which, for example, is a PC, the desired field force is set whereafter the control unit measures the impedance in the tissue and calculates the requisite pulse voltage from the generator. When a pulse is subsequently applied, the field force will always be constant, since the control unit always measures and adjusts the voltage from the generator before the pulse is generated.

With the system in Fig. 10 the sought-for effect will be achieved, e.g. to maintain a constant output voltage from the pulse generator independently of the impedance in the tissue. It also proves that a system according to Fig. 10 is excellent for measuring and assessing the treatment result achieved in HVIT. By measuring impedance and carrying out analysis of impedance change in the tissue after a pulse has been applied, the documentary support is given for assessing when the treatment is completed and no more pulses are needed or give a further positive effect. This method builds on the tissue model shown in Fig. 11a,b.

The impedance in tissue substantially consists of three components, the resistance in the extra cellular fluid, the resistance in the intra cellular fluid and the capacitance which is formed between the D.C. insulating effect of the cell membrane. In the model, we have combined the impedance effect of the cell core with the resistance in the intracellular fluid. At low frequencies, only current will flow through the extra cellular liquid and the impedance is determined substantially by R_{ev}. At medium-high frequencies, the capacitance of the cell membrane C_{cm} together with the resistance of the intracellular liquid, R_{iv}, will begin to effect the impedance. At high frequencies, substantially the components R_{ev} and R_{iv} will effect the impedance of the tissue. Thus, the result will be a frequency dependence in the impedance of the tissue which is largely dependent on the thickness of the cell membrane and the formation of the cells. At low frequencies, the impedance is approximately R_{ev} and at high frequencies $R_{ev}//R_{iv}$. The symbol // is employed to indicate that R_{ev} is connected in parallel with R_{iv}.

$$Z_{tissue} = R_{ev} // (R_{iv} + C_{cm})$$

Since the treatment with electric fields is intended to render the cell membrane permeable or to wholly destroy it, a clear indication will be obtained by measuring the change in C_{cm} as to whether the treatment is completed or not. When all cell membranes in the tissue are destroyed, no change of C_{cm} will take place any longer and the tissue is ready-treated.

Table 1 below illustrates a compilation of impedance measurements taken during the treatment of rats with tumors.

Table 1 Measured tissue impedance in ohm in rats with tumor

Frequency/Pulses	0 pulses	16 pulses	32 pulses	48 pulses	64 pulses
10 Hz	232.24	160.12	160.36	172.53	179.3
15 Hz	229.42	157.76	151.48	163.37	159.61
20 Hz	200.28	145.46	138.84	148.89	141.78
30 Hz	173.9	134.11	127.56	132.16	125.87
50 Hz	153.7	122.75	116.44	120	112.29
70 Hz	144.46	116.39	110.38	136.26	105.58
100 Hz	137.64	110.69	105.13	105.47	100.31
150 Hz	130.68	104.86	99.79	99.71	95.35
200 Hz	125.81	100.97	96.31	96.23	92.26
300 Hz	120.3	96.27	92.06	92.19	88.73
500 Hz	113.96	91.09	87.49	87.84	84.91
700 Hz	109.83	87.88	84.68	85.16	82.6
1000 Hz	105.88	85.03	82.2	83.03	80.62
1500 Hz	101.99	82.12	79.71	81.84	78.59
2000 Hz	99.34	80.27	78.02	79.54	77.69
3000 Hz	96.12	77.98	76.06	77.18	75.72
5000 Hz	92.28	75.4	73.81	74.85	73.71
7000 Hz	89.72	73.85	72.41	73.86	72.54
10000 Hz	87.38	72.45	71.14	73.52	71.43
15000 Hz	84.91	70.91	69.71	72.53	70.15
20000 Hz	83.18	69.75	68.62	71.51	69.17
30000 Hz	80.8	68.23	67.14	69.81	67.8
50000 Hz	77.73	66.26	65.28	68.24	65.97
70000 Hz	75.62	64.79	63.9	66.67	64.65
100000 Hz	73.01	63.01	62.11	64.62	62.93
150000 Hz	70.42	61.05	60.3	64.06	61.19
200000 Hz	68.3	59.37	58.76	61.93	59.65

It will be apparent from Table 1 that the impedance reduces at low and medium-high frequencies after treatment with pulses. The reduction principally takes place after the introductory 16 pulses and the change rapidly fades thereafter. Thus, the rat is substantially ready-treated already after the first 16 pulses and further treatment after 32 or 48 pulses gives no major change in C_{cm}. The measurement data in Table 1 indicates that the treatment is completed after 32 pulses. In order to confirm this assessment, the measured measurement values have been taken and treated as described below.

Table 2 shows the impedance change in per cent at different frequencies after the electric fields generated by 16 voltage pulses have passed through the tissue. In the Table, the change of the impedance is given in per cent which occurred each time when a series of electric fields generated by the voltage pulses has passed through the tissue.

Table 2 Impedance change in per cent after treatment with 16 pulses at a time

Frequency/Pulses	16 pulses	32 pulses	48 pulses	64 pulses
10 Hz	-31.05408	0.1033414	5.2402687	2.9150878
15 Hz	-31.23529	-2.737338	5.1826345	-1.638916
20 Hz	-27.37168	-3.305372	5.0179748	-3.55003
30 Hz	-22.88097	-3.766532	2.6451984	-3.617021
50 Hz	-20.13663	-4.1054	2.3162004	-5.016265
70 Hz	-19.43098	-4.160321	17.914994	-21.23771
100 Hz	-19.58006	-4.039523	0.2470212	-3.74891
150 Hz	-19.75819	-3.879706	-0.061218	-3.336394
200 Hz	-19.74406	-3.703998	-0.063588	-3.155552
300 Hz	-19.97506	-3.499584	0.1080632	-2.876143
500 Hz	-20.06845	-3.159003	0.3071253	-2.571078
700 Hz	-19.98543	-2.913594	0.4370391	-2.330875
1000 Hz	-19.6921	-2.672837	0.7839063	-2.276162
1500 Hz	-19.4823	-2.362977	2.08844	-3.186587
2000 Hz	-19.1967	-2.264949	1.5300987	-1.862291
3000 Hz	-18.87224	-1.997503	1.1652102	-1.518935
5000 Hz	-18.29215	-1.723017	1.1270048	-1.235371
7000 Hz	-17.68836	-1.604993	1.6161391	-1.471244
10000 Hz	-17.08629	-1.499199	2.7237354	-2.391852
15000 Hz	-16.48805	-1.413261	3.3211636	-2.802968
20000 Hz	-16.14571	-1.3585	3.4743929	-2.813176
30000 Hz	-15.55693	-1.34901	3.3044554	-2.487624
50000 Hz	-14.75621	-1.260774	3.8080535	-2.920365
70000 Hz	-14.32161	-1.176937	3.6630521	-2.671251
100000 Hz	-13.69675	-1.232708	3.4378852	-2.314751
150000 Hz	-13.30588	-1.065038	5.3393922	-4.075547
200000 Hz	-13.07467	-0.893119	4.6412884	-3.338214

The heading of the Table discloses the accumulated number of pulses of electric fields which have passed through the tissue. On each treatment occasion, a series of 16 pulses is passed through the tissue. That

disclosed in this paragraph for the table heading in Table 2 also applies to the table headings for Tables 3 and 4 used below.

It will be apparent from Table 2, in the same manner as Table 1, that the treatment may be discontinued after 32 pulses, since the impedance change fades dramatically. Table 3 below shows the mean value of the impedance change after different numbers of pulses. The mean value is formed from all measurement frequencies between 10 Hz and 200 kHz. In Table 3, it is clearly seen that the largest impedance change takes place after the first 16 pulses and only a slight change takes place on further treatment.

Table 3 Progressive change in per cent of impedance value at frequencies between 10 Hz-200 kHz

16 pulses	32 pulses	48 pulses	64 pulses
-19.9568	-2.424687	3.1275358	-3.366544

In Table 4, in mean value formation, frequencies below 100 Hz and frequencies over 10 kHz have been deleted. By deleting the lowest frequencies from the mean value, this prevents incorrect impedance values because of disturbance from the motorsystem of the body from influencing the result. The highest frequencies are deleted since the impedance change at these high frequencies is less when C_{cm} is changed and therefore does not contribute to an improved picture of the treatment result.

Table 4 Progressive change in per cent of impedance values at frequencies between 100 Hz-10 kHz

16 pulses	32 pulses	48 pulses	64 pulses
-20.78512	-2.943407	1.0007481	-2.663449

By allowing the control unit in Fig. 10 mathematically to treat and present the measured treatment result as described above, there will be obtained an apparatus which satisfies the wishes of controlling, in the treatment, the strength of the electric field in order to obtain a

basis for discontinuing the treatment at the correct moment and for being able to interpret the direct outcome of the treatment with the electric field.

From the foregoing description, it will be apparent that, in a very simple application of the present invention, the impedance of the tissue is determined at only one frequency. In such instance, a medium-high frequency, e.g. 15 kHz is selected. The inner impedance of the pulse generator is entered in the computer as a fixed value, whereby the impedance of the tissue is determined by a mathematical operation corresponding to that described above. In applications of the present invention, use is however made as a rule of many frequencies in order to eliminate the risks of any possible disruptions which may affect the measurement results.

The system illustrated in Fig. 10 includes means for adjusting the pulse voltage and its frequency content so that the electric field in the treated tissue is always constant regardless of impedance or resistance changes in the tissue. Such means also give a basis for assessing the achieved treatment effect in that it is of a structure which makes it possible to present, for example readily understandable values and graphs which, by mathematical operations, have been extracted from measured impedance or resistance data.

On practical application of the present invention in the embodiment where a radiation transmitter is employed, the radiation transmitter and the electrodes, in certain applications together with the electrode applicator and impedance measurement unit, together form a cohesive mechanical unit. This is of a design which makes it possible, in a restricted region of a human or an animal, to apply both the radiation transmitter and the electrodes in positions where the ionizing radiation is directed at the tissue which is being treated and where the electrodes are in positions in which electric fields between them pass through the tissue. In other embodiments, such means constitute separate parts which, together and where applicable temporarily, or for a lengthy period of time, form a system of devices of a composition corresponding to that described above for the apparatus 40.

The above detailed description has referred to but a limited number of embodiments of the present invention, but a person skilled in the art will readily perceive that the present invention encompasses a large number of embodiments without departing from the scope of the appended claims.

CLAIMS PCT/SE99/00511

1. An apparatus (60) for controlling the size of, configuration of and/or duration of electric fields which are generated by a voltage generator (1) between electrodes (6,15,16,24) included in the apparatus or between electrodes (6,15,16,24) connected to the apparatus where the apparatus includes means (4,5) for distributing the voltage pulses to the electrodes (6,15,16,24) for the formation of the electric fields, and where the electrodes are designed to be secured at a restricted region of a human or an animal or are designed to be inserted in said region, c h a r a c t e r i z e d in that said region excludes the skin of a human or an animal, that an impedance measurement unit (50) included in the apparatus is disposed, on treatment of tissue or organs adjacent or in said region, to determine the impedance and/or resistance between said electrodes; and that a control and converter unit (10) is included in the apparatus or is connected thereto in order, prior to each voltage pulse or chain of voltage pulses and based on the measurement impedance and/or resistance, to control the size of, number of, configuration of and/or duration of the voltages applied to the electrodes.

2. The apparatus as claimed in Claim 1, c h a r a c t e r i z e d in that the control and converter unit (10) includes a VDU (10a); that the control and converter unit is disposed, prior to the start of the generation by the voltage generator (1) of a pulse or chain of pulses, to show on the VDU (10a) the form of the pulse or chain of pulses calculated by the control and converter unit; and that means are included in said control and converter unit for manual or automatic acceptance of said calculated formation.

3. The apparatus as claimed in Claim 1 or 2, c h a r a c t e r - i z e d in that the electrodes (6,15,16,24) are common for the impedance measurement unit (50) and for said means (4,5) for emitting voltage pulses; or that separate electrodes (4,5) are provided for the impedance measurement unit and said means for emitting voltage pulses.

4. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6,15,16,24) are disposed, to be placed in a restricted region in a human or in an animal or in positions entailing that the electric fields pass through said region.

5. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the apparatus includes means (34) for supplying therapeutic substances, genetic material and/or ionizing radiation to said restricted region of a human or of an animal; or that the apparatus is designed to cooperate with such means (34).

6. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the apparatus includes sensors (8) for detecting electric fields formed by the electrodes (6,15,16,24); and that the sensors are connected to a registration and converter device (10) for calculating the size of the electric field strength in the treatment region; and that, for regulating the amplitude of the voltage pulses applied on the electrodes, the registration and converter device (10) is connected to the high voltage generator (1) and/or to means (2,3,4) connected inbetween the high voltage generator (1) and the electrodes (6,15,16,24).

7. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6) are disposed to be excited alternatingly and only two at a time.

8. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the apparatus includes sensors (14) for detecting the distance between the electrodes (6) in each pair of excited electrodes; and that said registration and converter device (10) includes means for adjusting the voltage between the electrodes (6) in each pair of excited electrodes based on the distance between the electrodes.

9. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6) are designed as needles (15) or stilettos (16).

10. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6,15,16,24) are wholly surrounded by an electrically insulating layer (17) or have an electrically insulating layer which at least leaves an electrically conductive tip of the electrodes uninsulated.

11. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that an electrode applicator (5,23) is provided for at least temporarily fixing the electrodes prior to the placing of the electrodes on or in the treatment region.

12. The apparatus as claimed in Claim 11, c h a r a c t e r i z e d in that the electrode applicator (23) is of a size and configuration which is adapted to the vessel, bodily aperture or bodily cavity where it is to be placed.

13. The apparatus as claimed in Claim 11, c h a r a c t e r i z e d in that the electrode applicator (5) includes a fixture (18) for fixing the electrodes (15,16) in a fixed pattern.

14. The apparatus as claimed in Claim 11, c h a r a c t e r i z e d in that the fixture (18) is provided with a number of holes for placing electrodes in a desired pattern on each treatment occasion.

15. The apparatus as claimed in Claim 11, c h a r a c t e r i z e d in that the electrode applicator (23) is provided with electrodes (24) placed on the applicator's surface; or that the electrodes (24) are placed in channels (25) discharging in apertures in the surface of the applicator and, by means of remote control, displaceable in the channels and at least partly out through the apertures in order to be inserted into the tissue around the applicator.

16. The apparatus as claimed in any of Claims 1-10, c h a r a c t e r i z e d in that the apparatus includes at least one cannula (19) each one disposed for temporarily enclosing an electrode.

17. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6,15,16,24) consist of radioactive material or are designed with apertures for accommodating radioactive preparations (21).

18. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6,15,16,24) are coated with a layer (27) of porous material for accommodating therapeutic substances (28).

Fig. 1

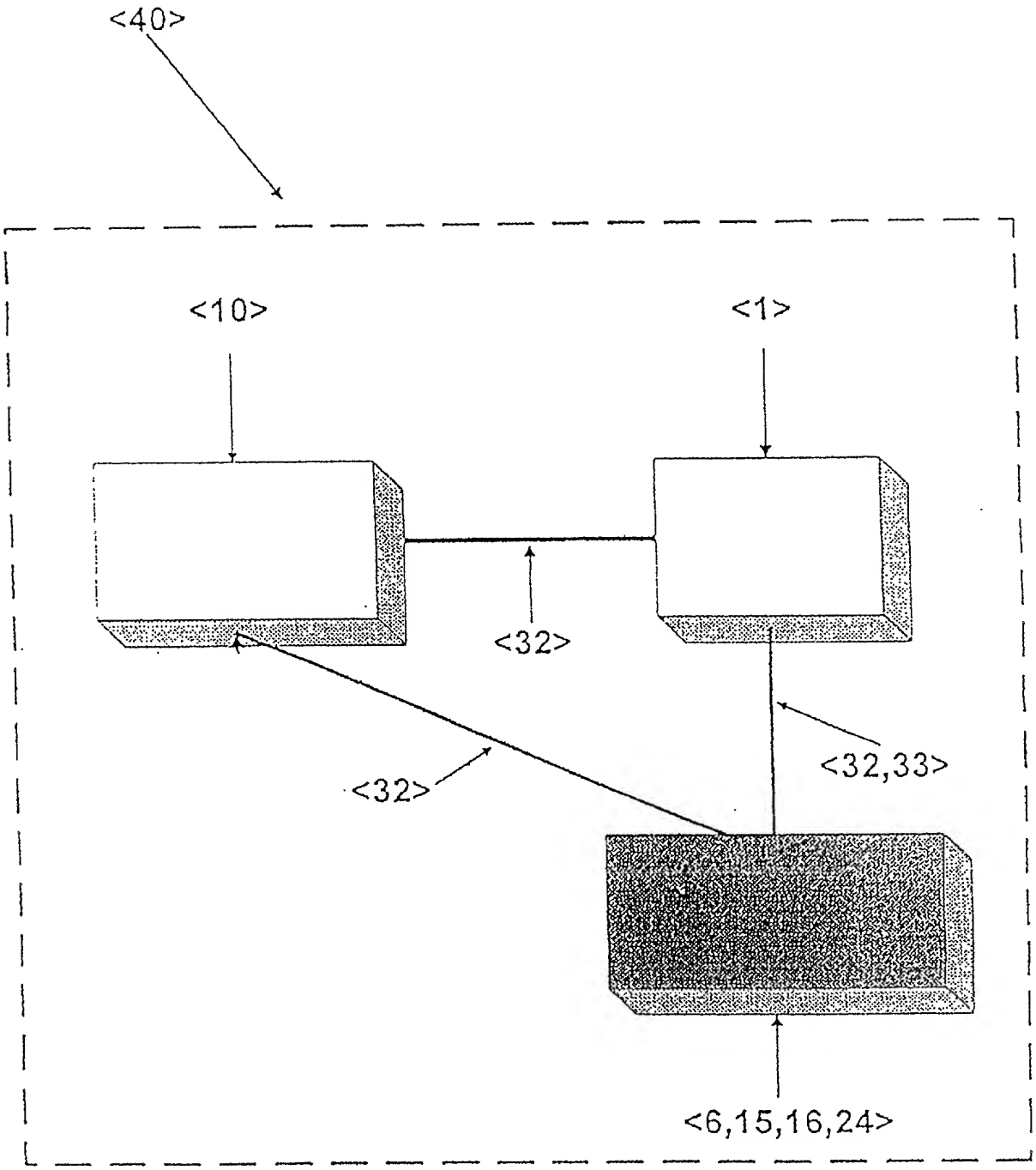


Fig. 2

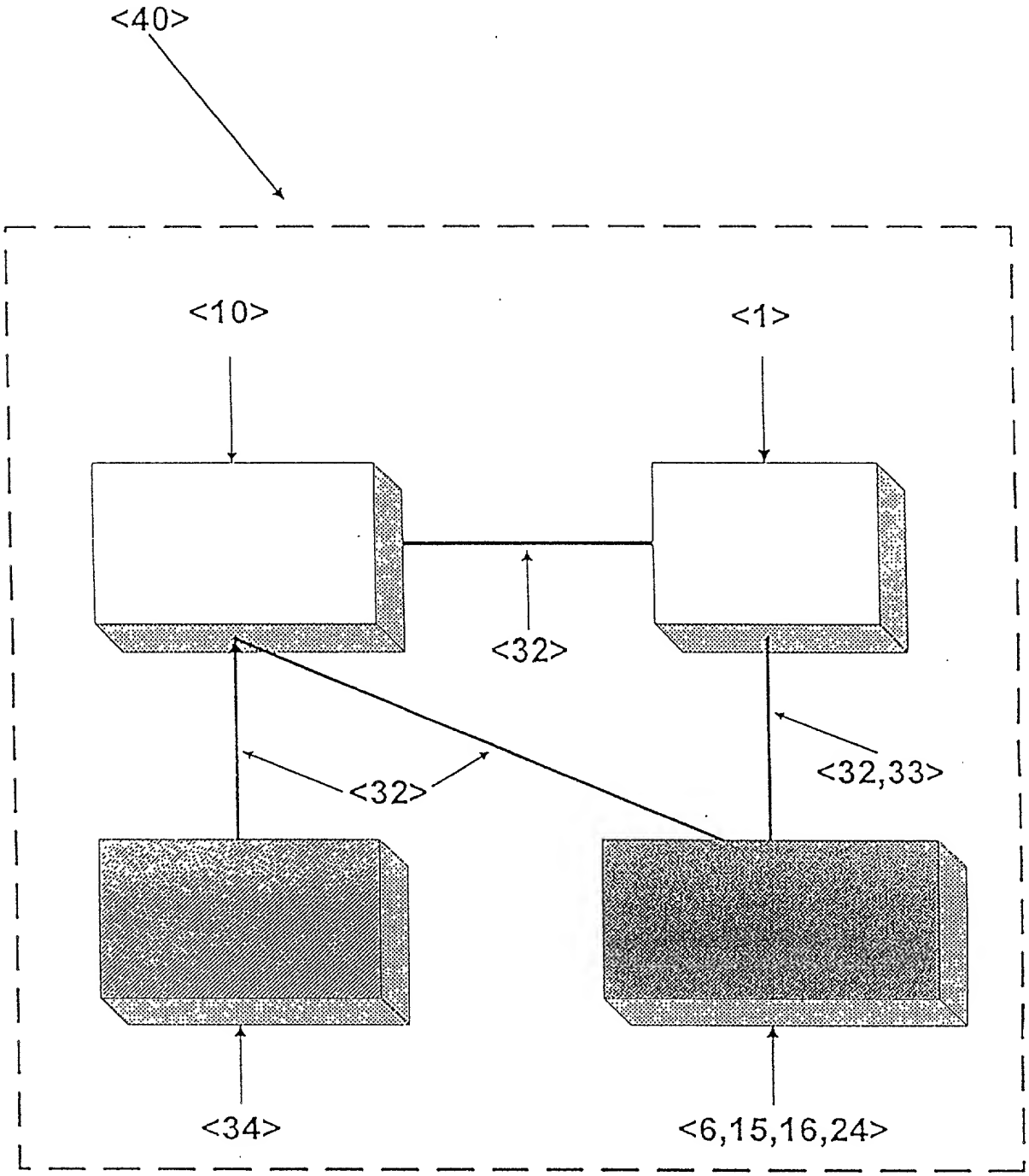


Fig. 3

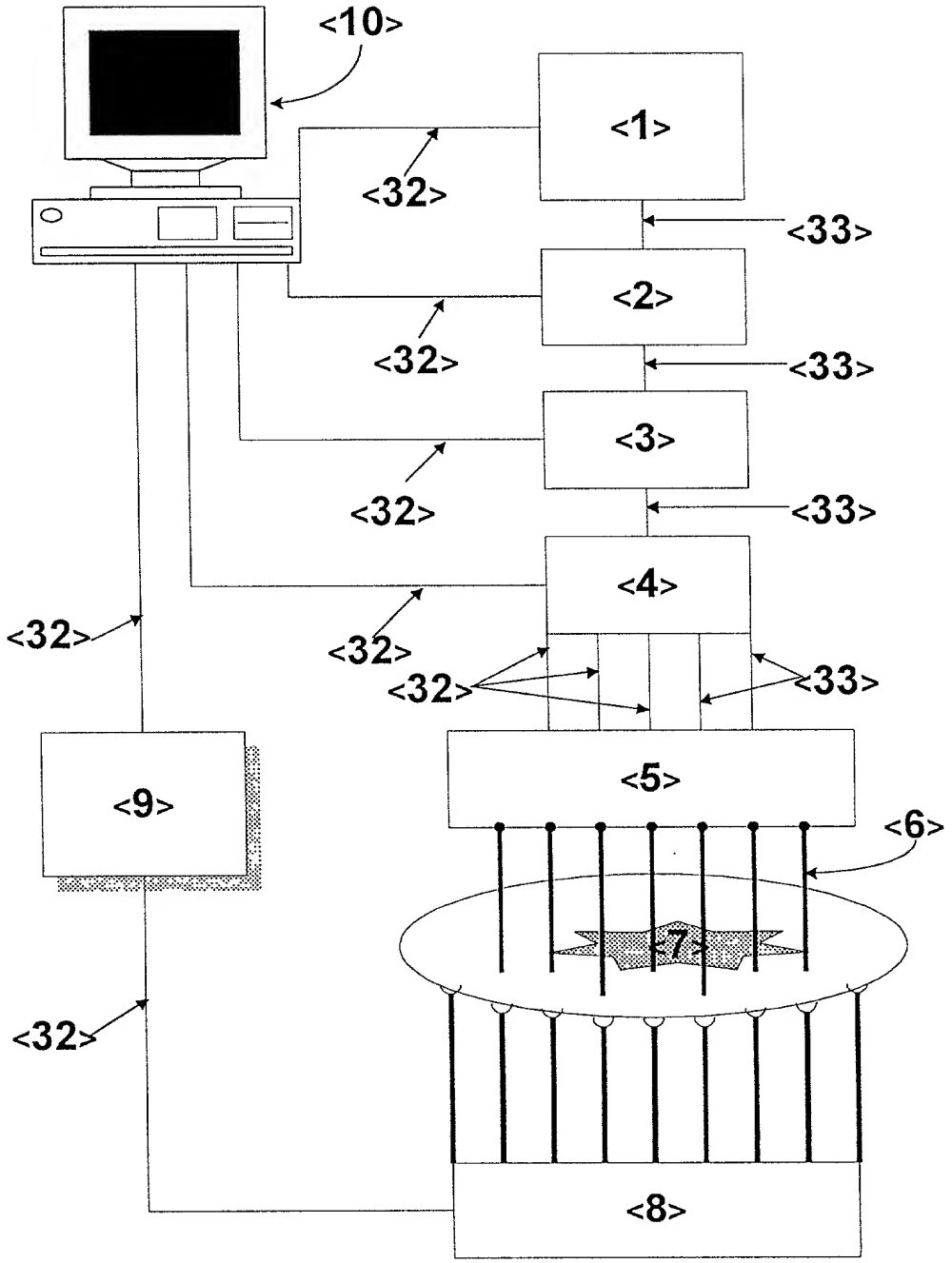
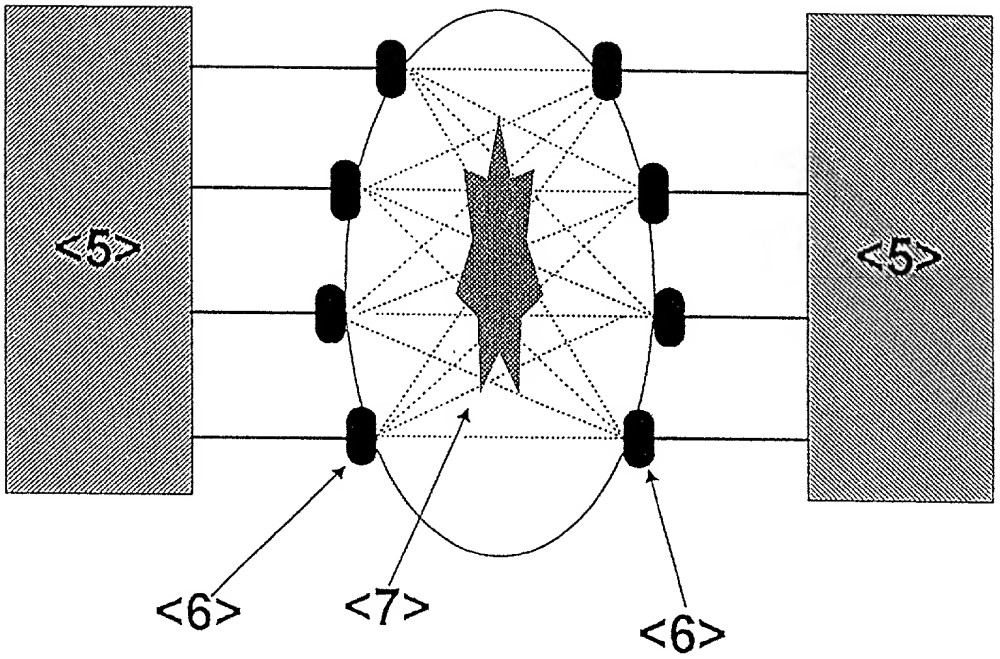


Fig. 4 a,b



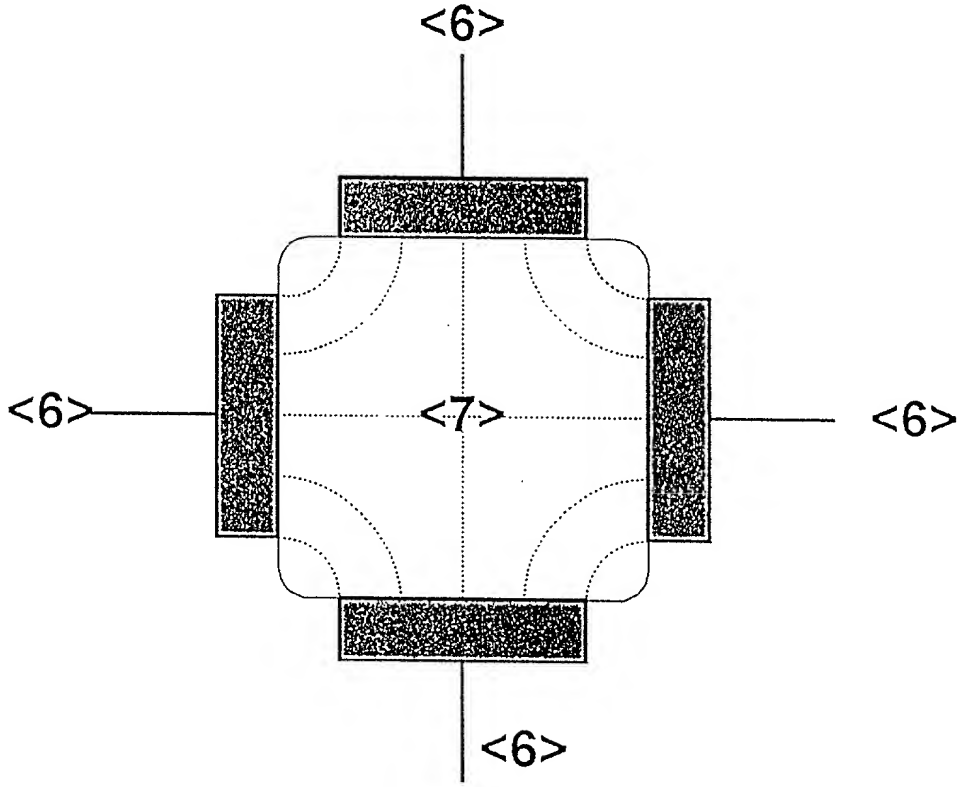


Fig. 4 c,d

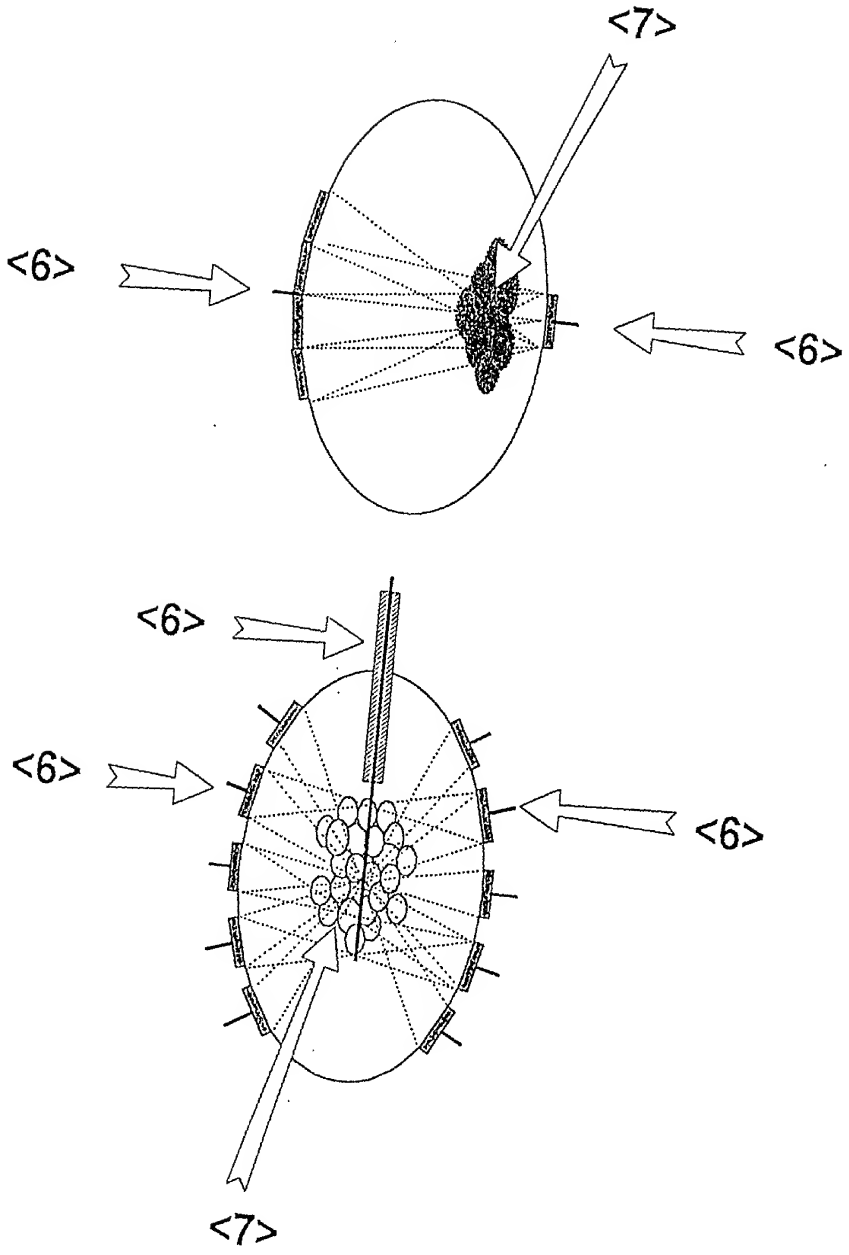
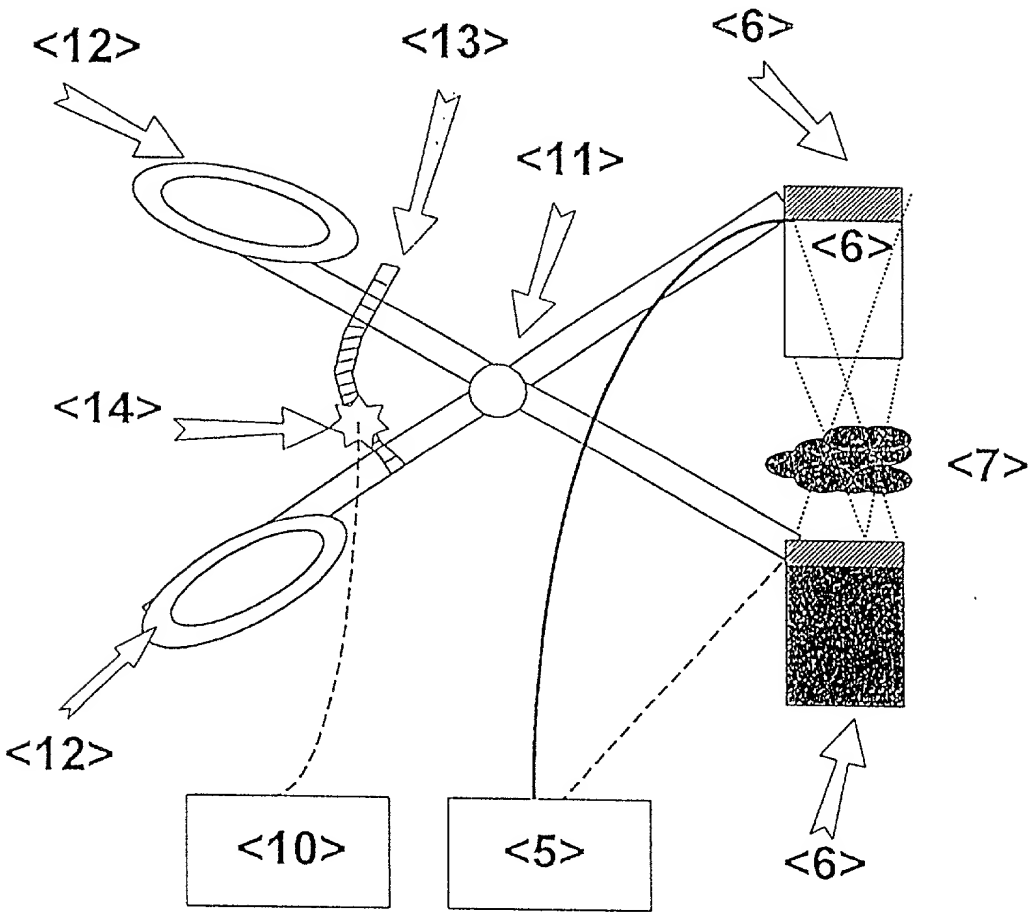


Fig. 5



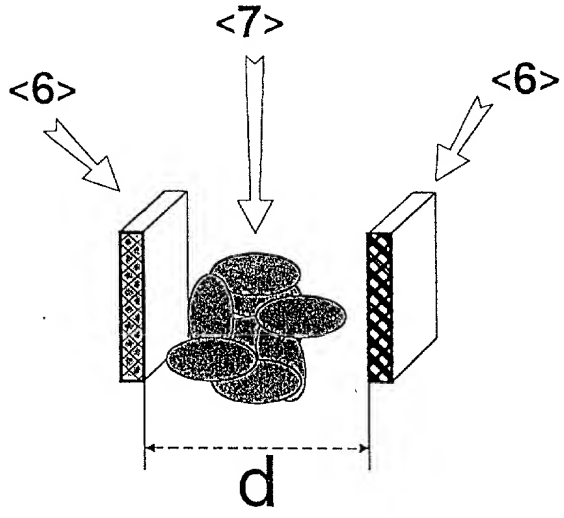


Fig. 6 a

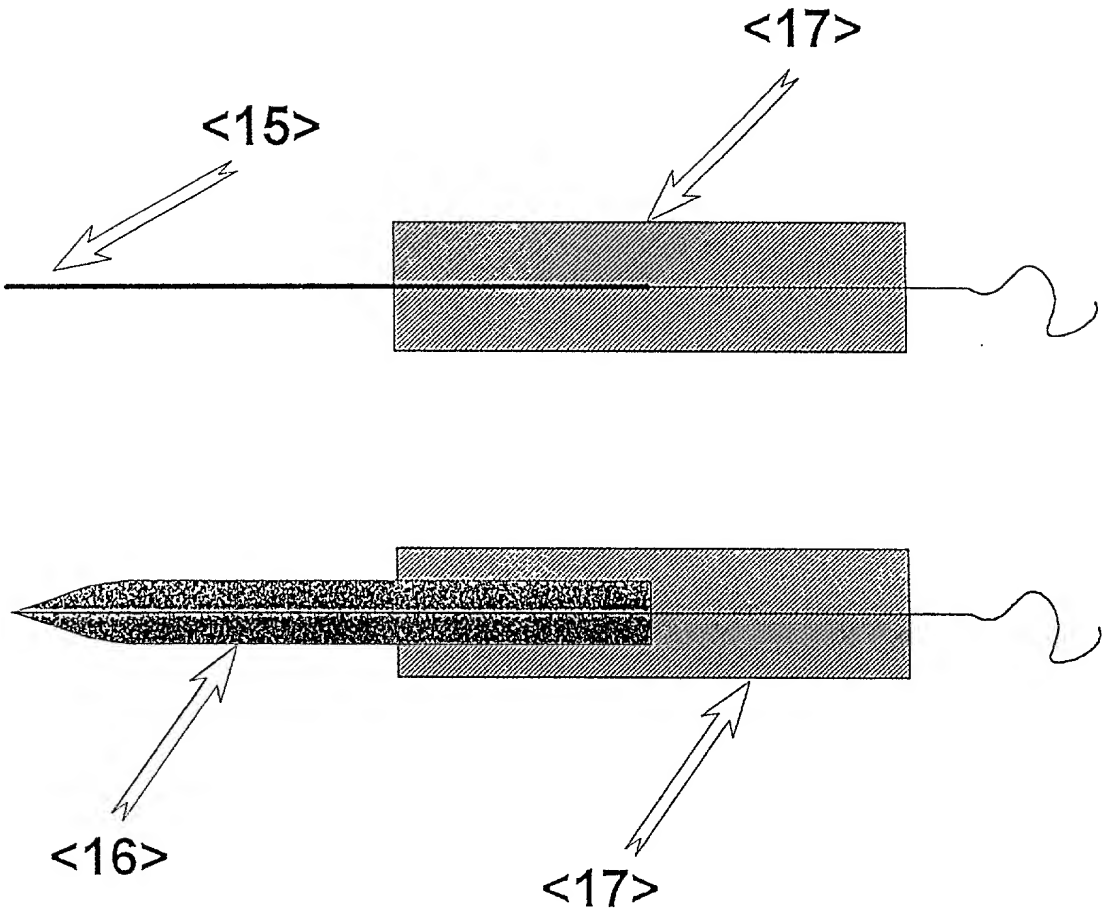


Fig. 6 b

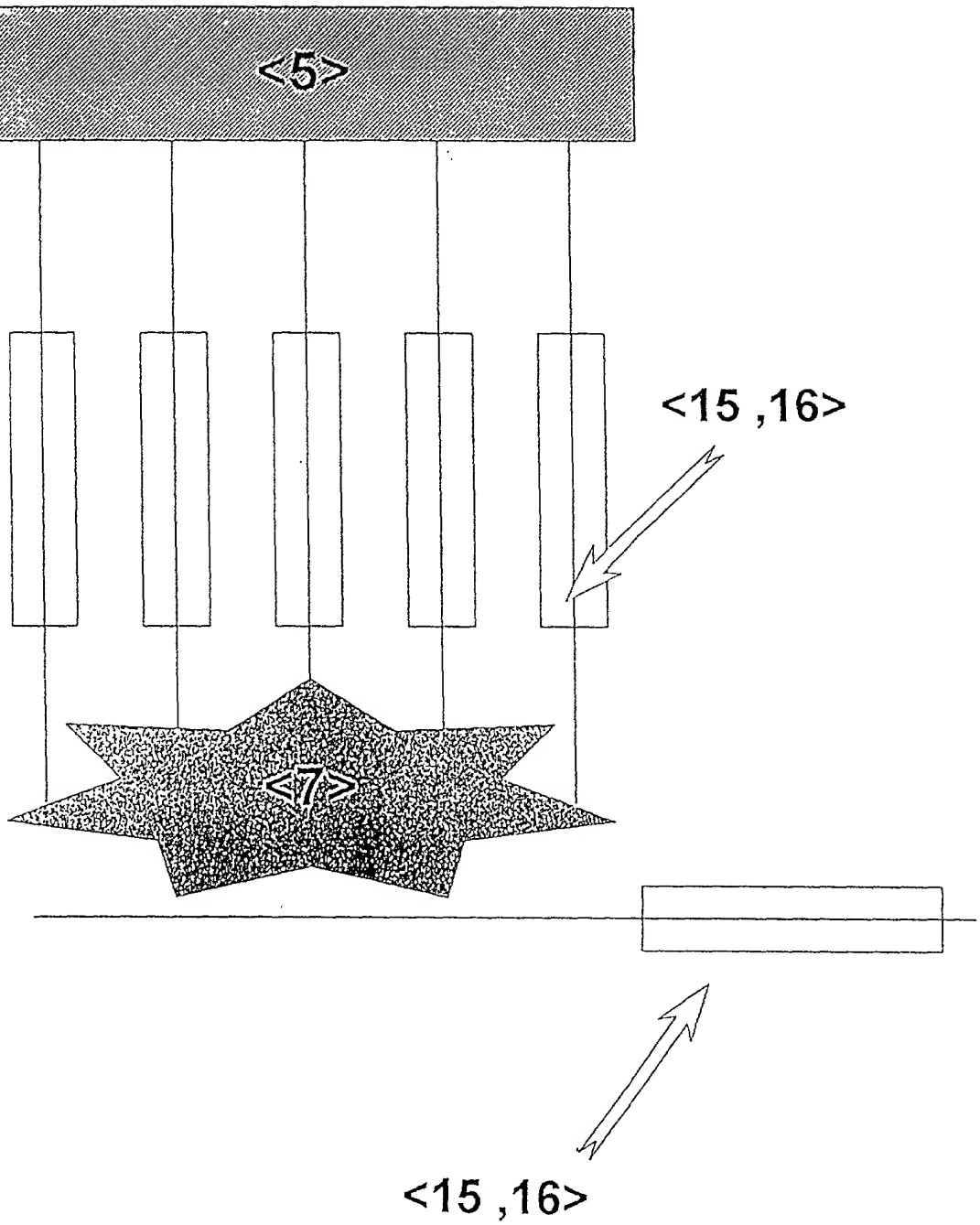


Fig. 6 c

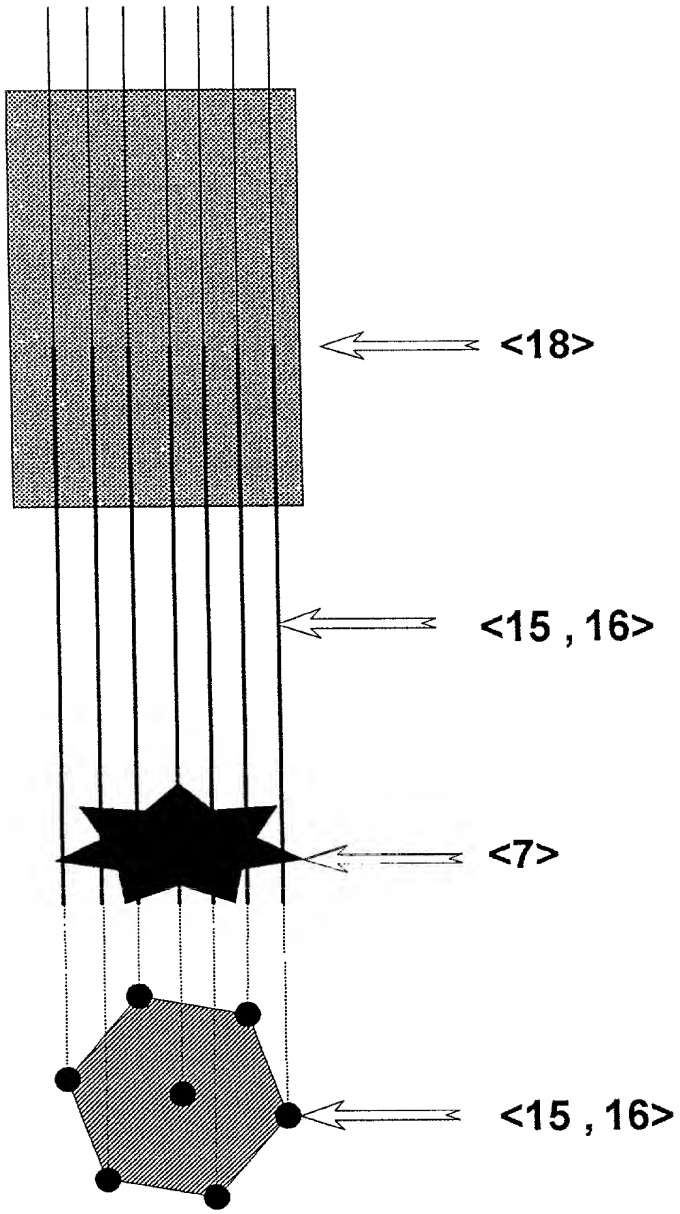


Fig. 6 d

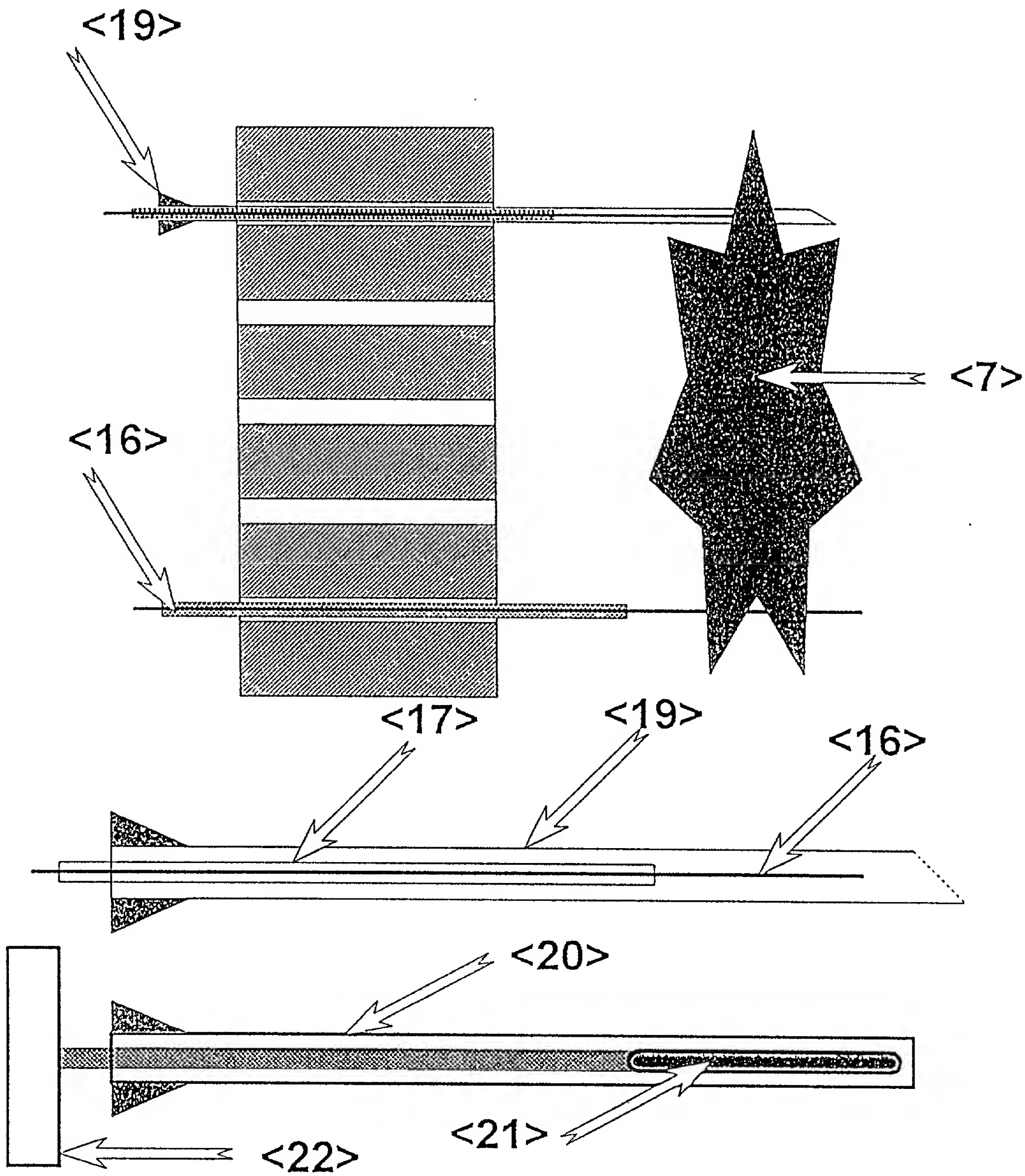


Fig.7 a-c

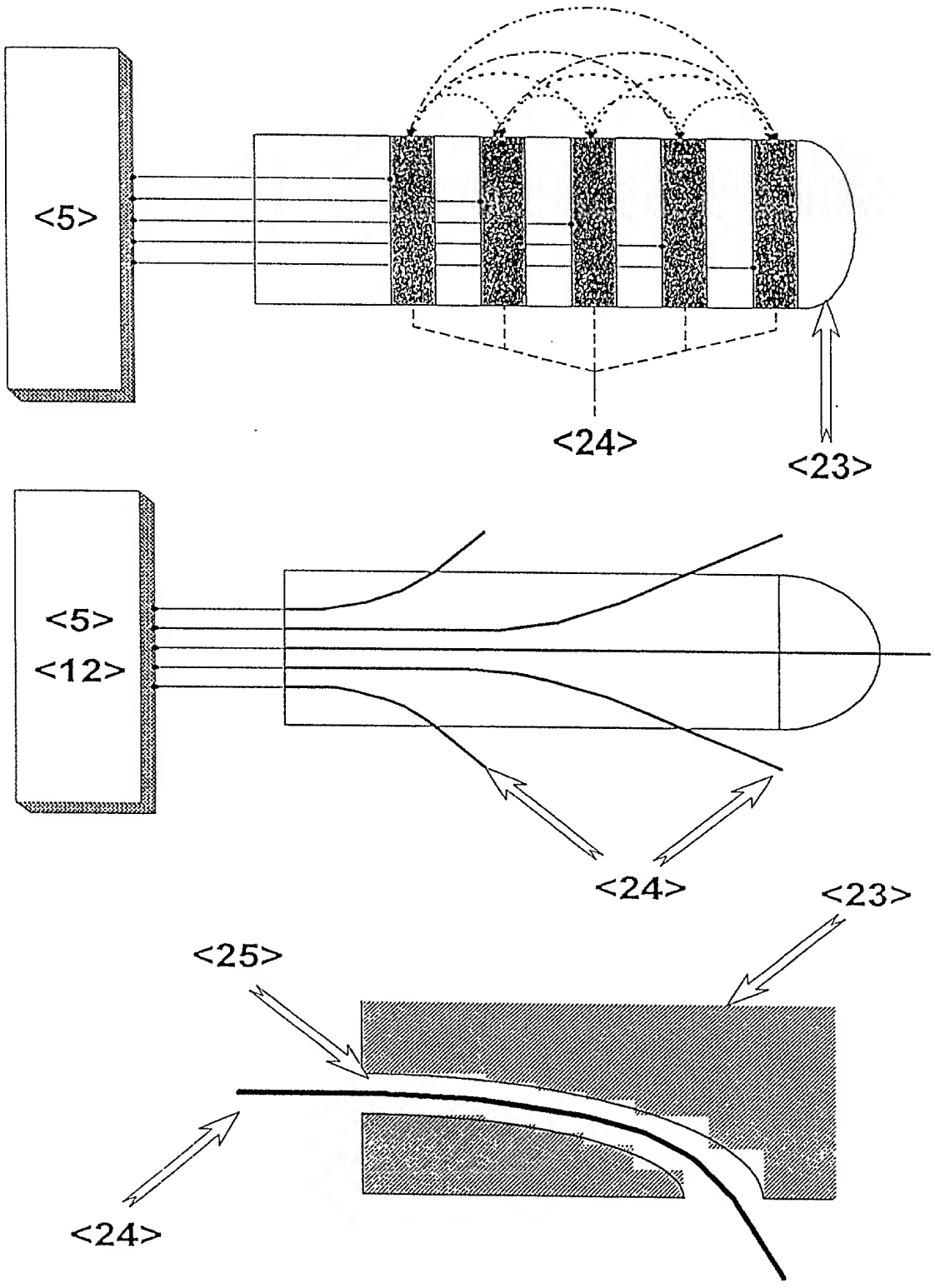


Fig. 8

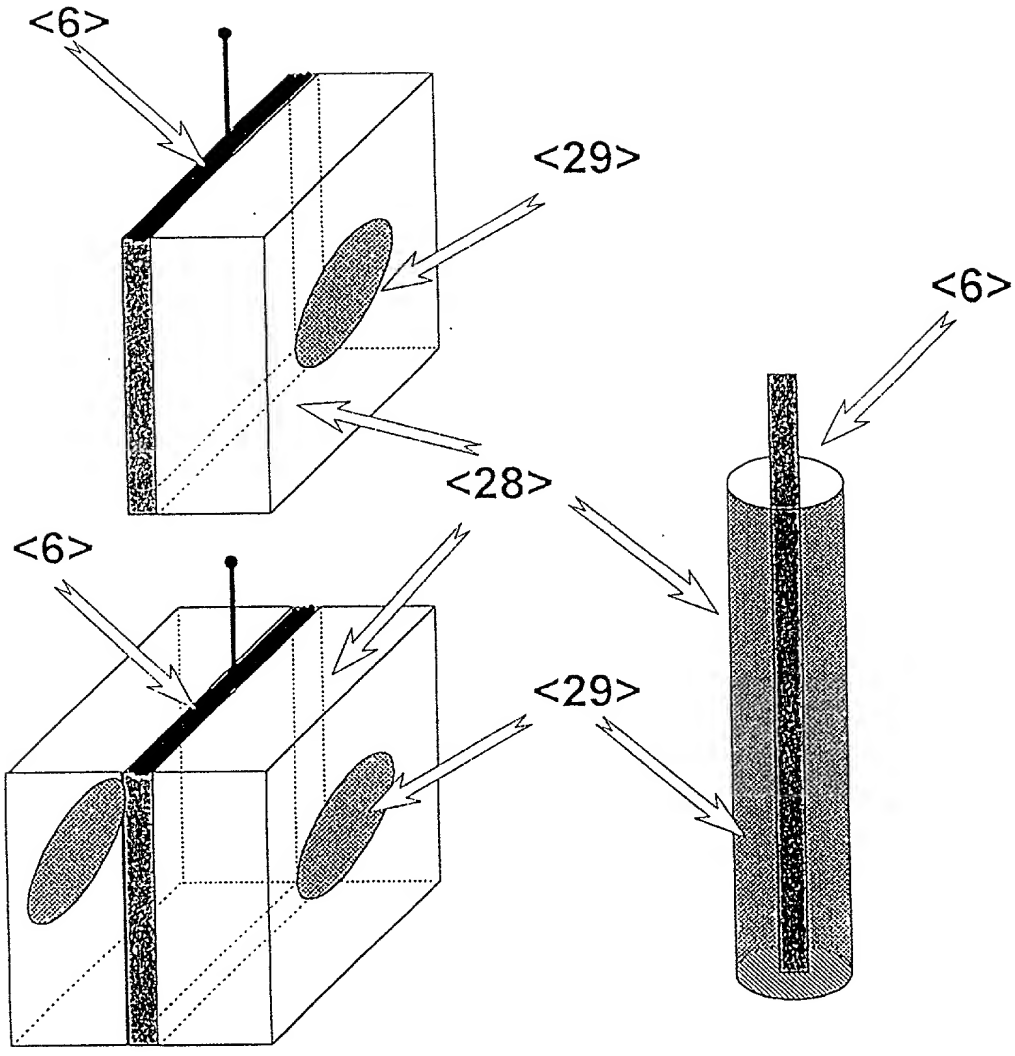


Fig. 9 a-e

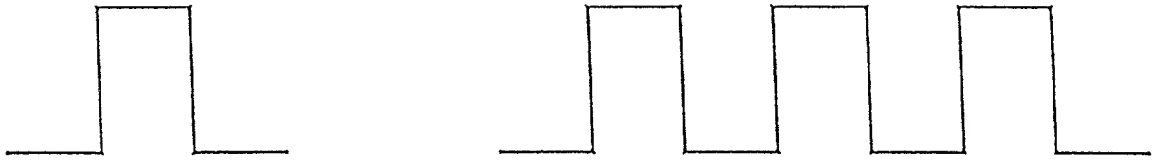


Fig. 9 a

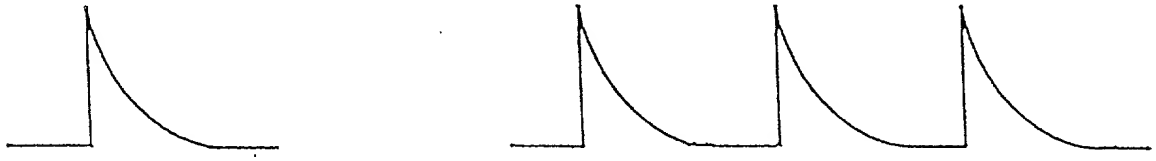


Fig 9 b

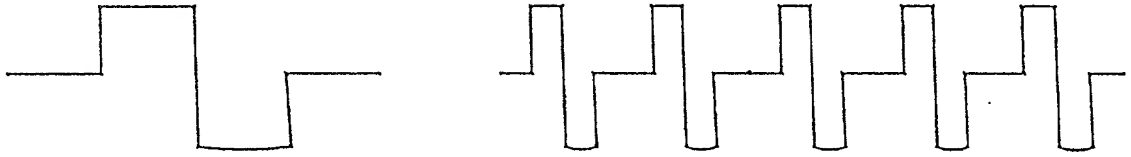


Fig 9 c

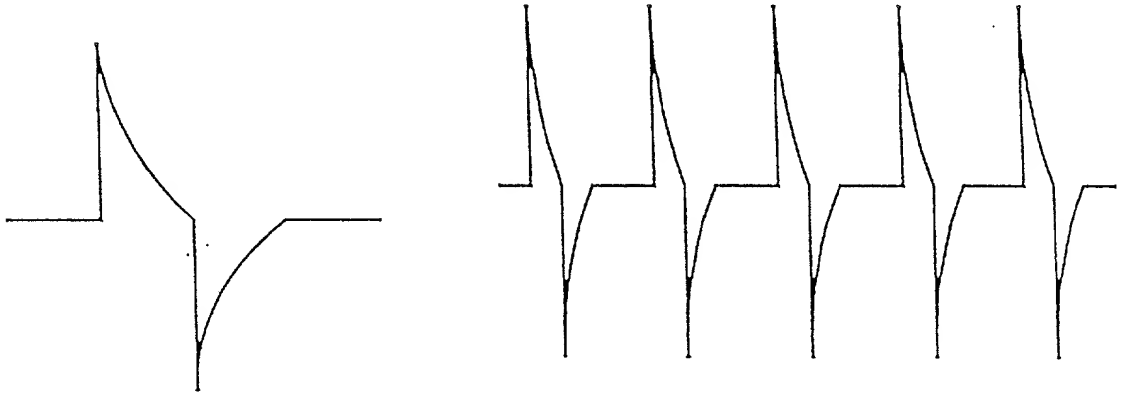


Fig. 9 d

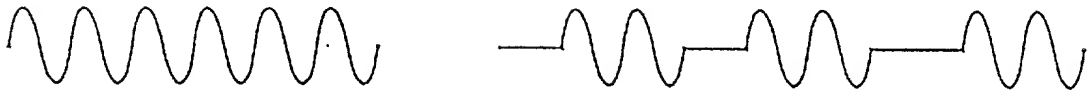


Fig 9 e

Fig. 10

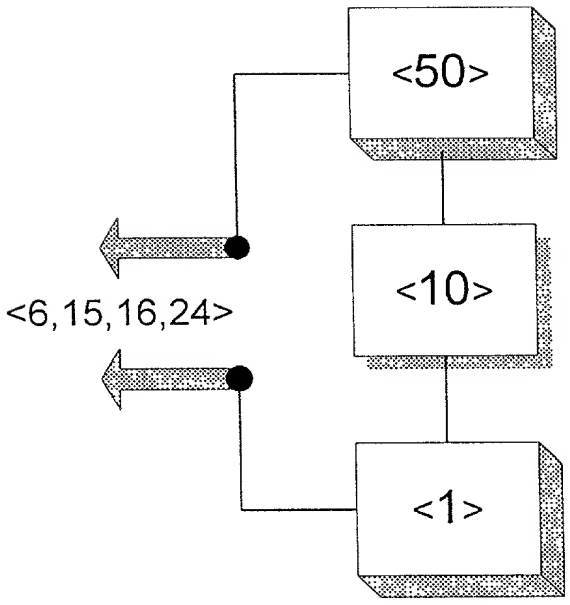


Fig. 11 a,b

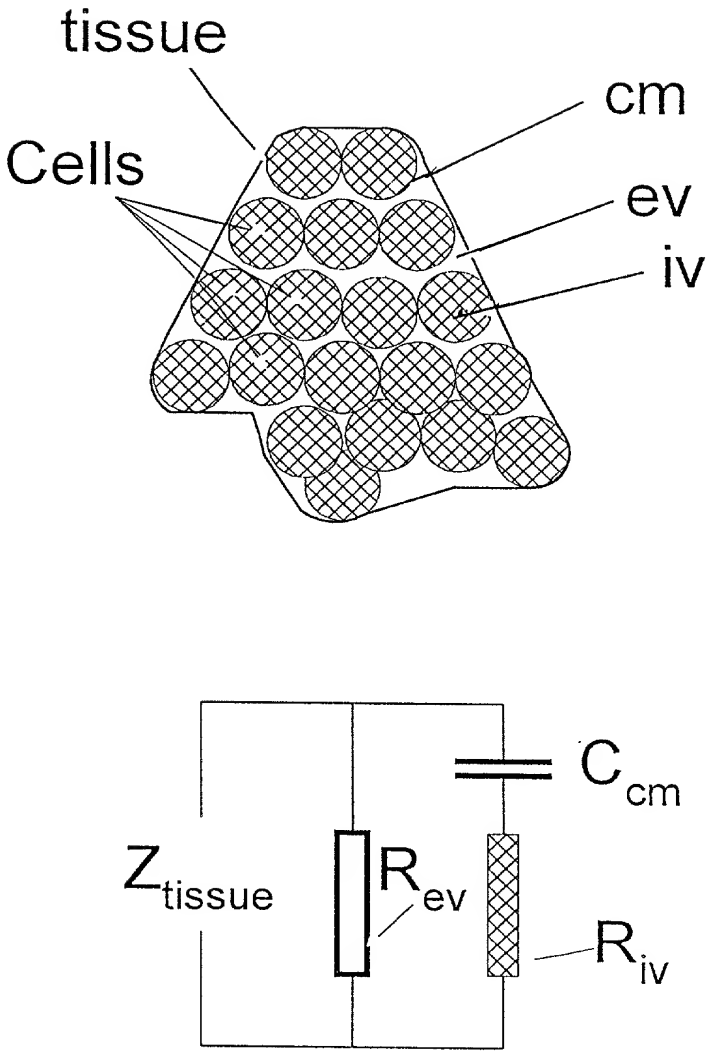
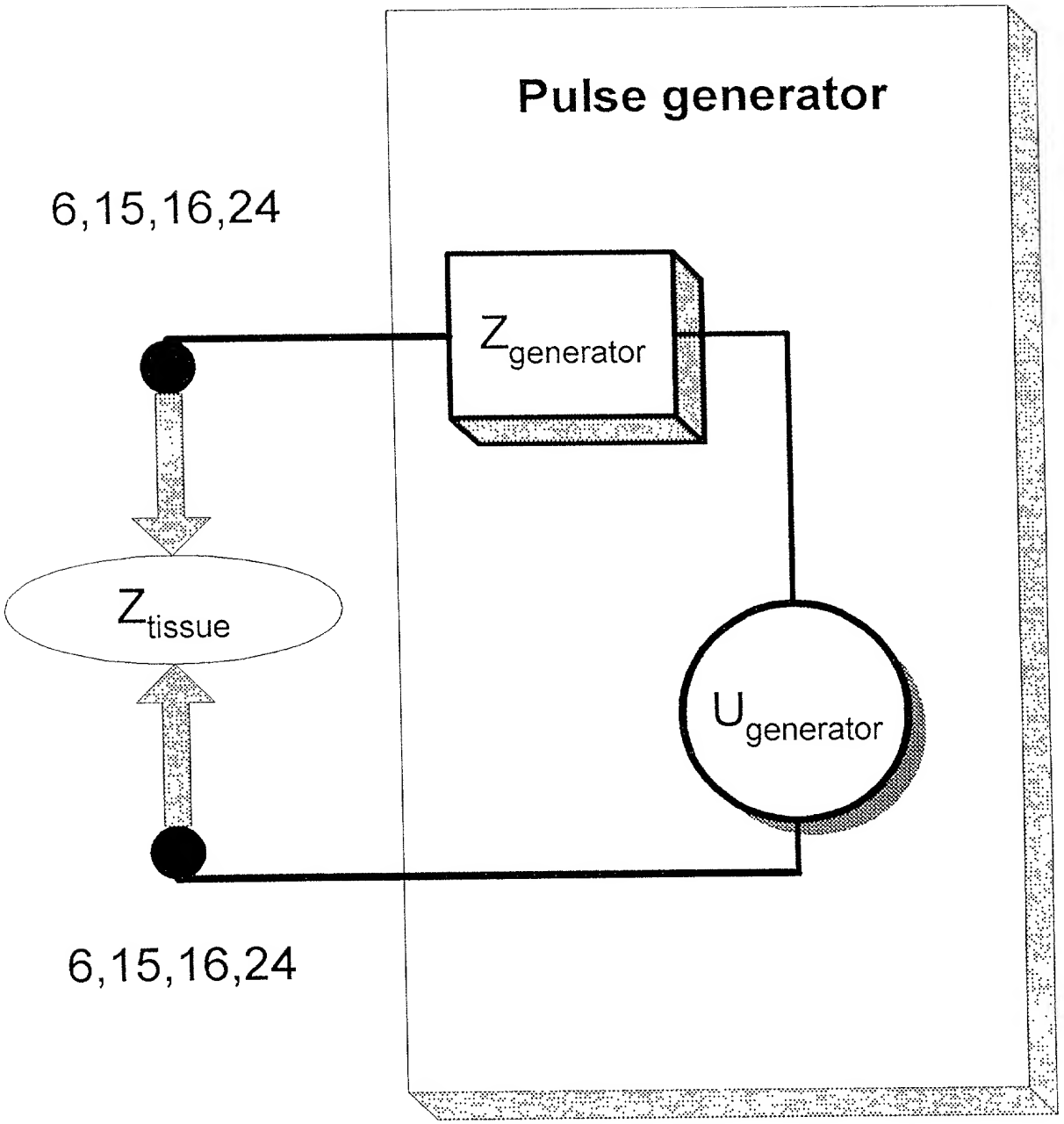


Fig. 12


Pulse generator
6,15,16,24
$Z_{generator}$
Z_{tissue}
$U_{generator}$
6,15,16,24

Practitioner's Docket No. U 012894-7 ***PATENT***

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION, OR C-I-P)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type:

(check one applicable item below)

[X] original.
[ ] design.
[ ] supplemental.

NOTE: If the declaration is for an International Application being filed as a divisional, continuation or continuation-in-part application, do not check next item; check appropriate one of last three items.

[X] national stage of PCT.

NOTE: If one of the following 3 items apply, then complete and also attach ADDED PAGES FOR DIVISIONAL, CONTINUATION OR C-I-P.

NOTE: See 37 CFR 1.63(d) (continued prosecution application) for use of a prior nonprovisional application declaration in the continuation or divisional application being filed on behalf of the same or fewer of the inventors named in the prior application.

[ ] divisional.
[ ] continuation.

NOTE: Where an application discloses and claims subject matter not disclosed in the prior application, or a continuation or divisional application names an inventor not named in the prior application, a continuation-in-part application must be filed under 37 CFR 1.53(b) (application filing requirements-nonprovisional application).

[ ] continuation-in-part (C-I-P).

INVENTORSHIP IDENTIFICATION

WARNING: If the inventors are each not the inventors of all the claims, an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.

My residence, post office address and citizenship are as stated below, next to my name. I believe that I am the original, first and sole inventor *(if only one name is listed below)* or an original, first and joint inventor *(if plural names are listed below)* of the subject matter that is claimed, and for which a patent is sought on the invention entitled:

EXPRESS MAIL LABEL NO.: EL386270495US

TITLE OF INVENTION

An Apparatus for Controlling the Generation of Electric Fields

SPECIFICATION IDENTIFICATION

The specification of which:

(complete (a), (b), or (c))

(a) [ ] is attached hereto.

NOTE: "The following combinations of information supplied in an oath or declaration filed on the application filing date with a specification are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 CFR 1.63:

"(1) name of inventor(s), and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration on filing;

"(2) name of inventor(s), and attorney docket number which was on the specification as filed; or

"(3) name of inventor(s), and title which was on the specification as filed."

Notice of July 13, 1995 (1177 O.G. 60).

(b) [ ] was filed on _____, as [ ] Serial No. 0 / _____ or
[ ] _____ and was amended on _____ *(if applicable).*

NOTE: Amendments filed after the original papers are deposited with the PTO that contain new matter are not accorded a filing date by being referred to in the declaration. Accordingly, the amendments involved are those filed with the application papers or, in the case of a supplemental declaration, are those amendments claiming matter not encompassed in the original statement of invention or claims. See 37 CFR 1.67.

NOTE: "The following combinations of information supplied in an oath or declaration filed after the filing date are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 CFR 1.63:

"(1) name of inventor(s), and application number (consisting of the series code and the serial number; e.g.,08/123,456);

"(2) name of inventor(s), serial number and filing date;

"(3) name of inventor(s) and attorney docket number which was on the specification as filed;

"(4) name of inventor(s), title which was on the specification as filed and filing date;

"(5) name of inventor(s), title which was on the specification as filed and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration; or

"(6) name of inventor(s), title which was on the specification as filed and accompanied by a cover letter accurately identifying the application for which it was intended by either the application number (consisting of the series code and the serial number; e.g.,08/123,456), or serial number and filing date. Absent any statement(s) to the contrary, it will be presumed that the application filed in the PTO is the application which the inventor(s) executed by signing the oath or declaration."

Notice of July 13, 1995 (1177 O.G. 60).

(c) [X] was described and claimed in PCT International Application No. PCT/SE99/00511 filed on March 30, 1999 and as amended under PCT Article 19 on April 18, 2000 *(if any)*.

SUPPLEMENTAL DECLARATION (37 CFR 1.67(b))

(complete the following where a supplemental declaration is being submitted)

[ ] I hereby declare that the subject matter of the

[ ] attached amendment
[ ] amendment filed on _____.

was part of my/our invention and was invented before the filing date of the original application, above identified, for such invention.

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in 37, Code of Federal Regulations, § 1.56,

(also check the following items, if desired)

[ ] and which is material to the examination of this application, namely, information where there is a substantial likelihood that a reasonable Examiner would consider it important in deciding whether to allow the application to issue as a patent, and

[ ] in compliance with this duty, there is attached an information disclosure statement, in accordance with 37 CFR 1.98.

PRIORITY CLAIM (35 U.S.C. § 119(a)-(d))

NOTE: "The claim to priority need be in no special form and may be made by the attorney or agent if the foreign application is referred to in the oath or declaration as required by § 1.63. The claim for priority and the certified copy of the foreign application specified in 35 U.S.C. § 119(b) must be filed in the case of an interference (§ 1.630), when necessary to overcome the date of a reference relied upon by the examiner, when specifically required by the examiner, and in all other situations, before the patent is granted. If the claim for priority or the certified copy of the foreign application is filed after the date the issue fee is paid, it must be accompanied by a petition requesting entry and by the fee set forth in § 1.17(i). If the certified copy is not in the English language, a translation need not be filed except in the case of interference; or when necessary to overcome the date of a reference relied upon by the examiner; or when specifically required by the examiner, in which event an English language translation must be filed together with a statement that the translation of the certified copy is accurate." 37 CFR 1.55(a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(complete (d) or (e))

(d) [ ] no such applications have been filed.

(e) [X] such applications have been filed as follows.

NOTE: Where item (c) is entered above and the International Application which designated the U.S. itself claimed priority check item (e), enter the details below and make the priority claim.

PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS APPLICATION AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. § 119(a)-(d)

COUNTRY (OR INDICATE IF PCT)	APPLICATION NUMBER	DATE OF FILING DAY, MONTH, YEAR	PRIORITY CLAIMED UNDER 35 USC 119
Sweden	9801139-8	31 March 1998 ✓	[X]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S)
(35 U.S.C. § 119(e))

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

PROVISIONAL APPLICATION NUMBER	FILING DATE
_______ / ____________________	__________
_______ / ____________________	__________
_______ / ____________________	__________

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S) UNDER 35 U.S.C. § 120

[ ] The claim for the benefit of any such applications are set forth in the attached ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR CONTINUATION-IN-PART (C-I-P) APPLICATION.

ALL FOREIGN APPLICATION(S), *IF ANY*, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

____

____

____

NOTE: *If the application filed more than 12 months from the filing date of this application is a PCT filing forming the basis for this application entering the United States as (1) the national stage, or (2) a continuation, divisional, or continuation-in-part, then also complete ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR C-I-P APPLICATION for benefit of the prior U.S. or PCT application(s) under 35 U.S.C. § 120.*

POWER OF ATTORNEY

I hereby appoint the following practitioner(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

(list name and registration number)

JOSEPH H. HANDELMAN, 26179

JOHN RICHARDS, 31053

RICHARD J. STREIT, 25765

ALAN K. ROBERTS, 17777

S. DELVALLE GOLDSMITH, 14383

PETER. GALLOWAY, 27885

IAIN C. BAILLIE, 24090

THOMAS F. PETERSON, 24790

RICHARD P. BERG, 28145

JULIAN H. COHEN, 20302

WILLIAM R. EVANS, 25858

JANET I CORD, 33778

CLIFFORD J. MASS, 30086

(Check the following item, if applicable)

[X] Attached, as part of this declaration and power of attorney, is the authorization of the above-named practitioner(s) to accept and follow instructions from my representative(s).

SEND CORRESPONDENCE TO

Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

DIRECT TELEPHONE CALLS TO:
(Name and telephone number)

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon

SIGNATURE(S)

NOTE: Carefully indicate the family (or last) name, as it should appear on the filing receipt and all other document.

Full name of sole or first inventor

1-00 Bertil R. R. PERSSON
(Given Name) *(Middle Initial or Name)* *Family (Or Last Name*

Inventor's signature Bertil Persson

Date July 17, 2000 **Country of Citizenship** SWEDEN

Residence Angantyrsgränd 19, SE-224 75 LUND SEX

Post Office Address Same as above

Full name of second joint inventor, if any

2-00 Bernt J. BÖHMER
(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature Bernt J. Böhmer

Date July 17, 2000 **Country of Citizenship** SWEDEN

Residence Bålabäcksvägen 1, SE-240 36 STEHAG SEX

Post Office Address Same as above

Full name of third joint inventor, if any

3-00 Bo H.G. THORVINGER
(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature Bo H.G. Thorvinger

Date July 17, 2000 **Country of Citizenship** SWEDEN

Residence Humlebäcksgatan 43, SE-216 20 MALMÖ SEX.

Post Office Address Same as above

(check proper box(es) for any of the following added page(s) that form a part of this declaration)

[ ] **Signature** for fourth and subsequent joint inventors. *Number of pages added* _____

* * *

[ ] **Signature** by administrator(trix), executor(trix) or legal representative for deceased or incapacitated inventor. *Number of pages added* _____

* * *

[ ] **Signature** for inventor who refuses to sign or cannot be reached by person authorized under 37 CFR 1.47. *Number of pages added* _____

* * *

[ ] Added page for **signature** by one joint inventor on behalf of deceased inventor(s) where legal representative cannot be appointed in time. (37 CFR 1.47)

* * *

[ ] Added pages to combined declaration and power of attorney for divisional, continuation, or continuation-in-part (C-I-P) application.

[ ] Number of pages added _____

* * *

[ ] Authorization of practitioner(s) to accept and follow instructions from representative.

(If no further pages form a part of this Declaration, then end this Declaration with this page and check the following item)

[X] This declaration ends with this page.